STEROIDAL REARRANGEMENTS

THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

IN

CHEMISTRY

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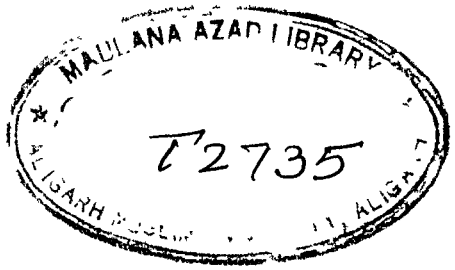
INDIA

1984



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Date 16.4.1984

This is to certify that the work embodied in this thesis entitled, "Steroidal Rearrangements" is the original work of Mr. Shakir Husain carried out under my supervision. The thesis is suitable for submission for the award of the degree of Doctor of Philosophy in Chemistry.

Shafiullah

(SHAFIULLAH)

To

The Suppressed & Oppressed
Class of the World

Acknowledgements

I express my gratitude to Dr. Shafiullah for his valuable guidance and supervision throughout this research work. I am extremely grateful to Professor M.S. Ahmad for his generous help and to Professor W. Rahman, Chairman, Department of Chemistry, for providing necessary facilities.

I would like to express my thankfulness to my research colleagues for their cooperation. Finally, I acknowledge the University Grants Commission, New Delhi for financial assistance.

Shakir Husain

(SHAKIR HUSAIN)

Contents

Summary

Part One

Reactions of Nitrosteroids

(A) Allylic bromination and dehydrobromination of steroidal-6-nitroolefins

Halogenation of ketones at α-position and subsequent dehydrohalogenation by base is frequently employed to create unsaturated centres adjacent to ketonic functions. Such operations have been of immense utility in the field of steroids. No such attempts have been made with unsaturated nitro compounds. We considered it expedient to prepare some nitro steroids with bromines at α- and β-positions and subject some of them to dehydrohalogenation. In this connection, allylic bromination of 3β-acetoxy-6-nitrocholest-5-ene (I), 3β-chloro-6-nitrocholest-5-ene (II) and 6-nitrocholest-5-ene (III)[a] was carried out. The products obtained were characterized on the basis of their spectral and chemical properties.

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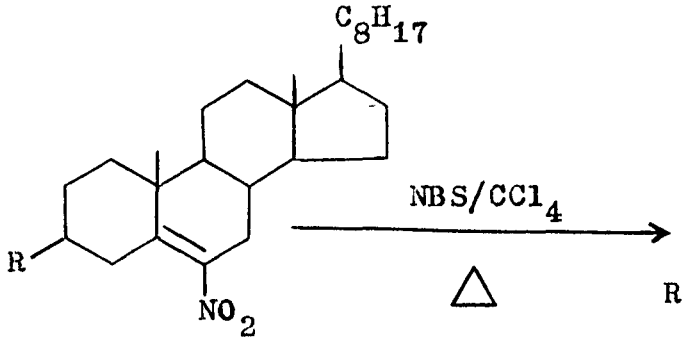
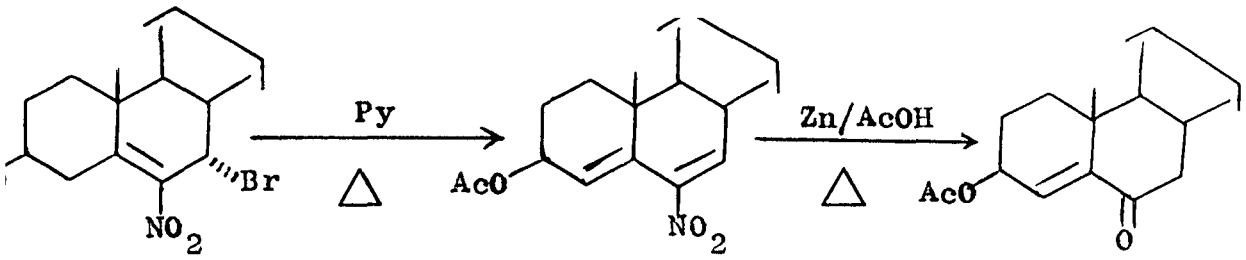
a. Allylic bromination of nitrosteroids
Ind. J. Chem., 1983, 22B(1), 71.

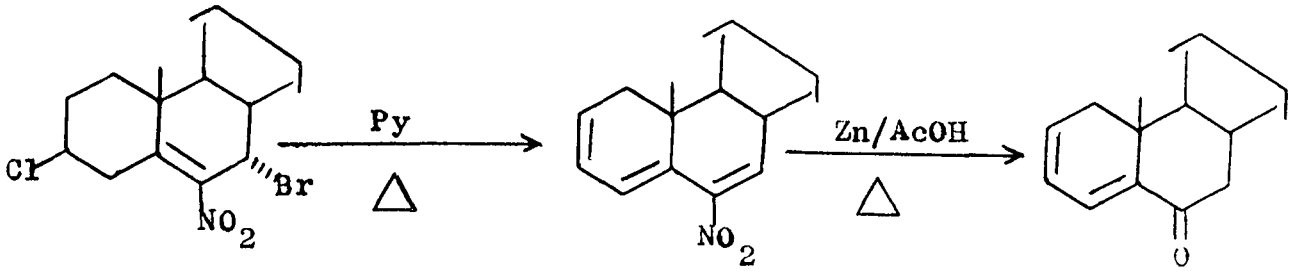


	R
(I)	OAc
(II)	Cl
(III)	H

	R	X
(IV)	OAc	H
(V)	Cl	H
(VI)	H	Br



(I) (VII) (VIII)



(II) (IX) (X)

(B) Oxidation of steroidal-6-nitro olefins with lead (IV) acetate

A survey of literature reveals that no work on oxidation of steroidal nitroolefins with lead (IV) acetate has been reported. Lead (IV) acetate in glacial acetic acid reacts with simple alkenes, ketones, oximes, alcohols and lactones to provide a variety of products.

The present work is concerned with the reaction of some of the easily accessible steroidal nitroolefins such as 3β-chloro-6-nitrocholest-5-ene (II)[b], 3β-acetoxy-6-nitrocholest-5-ene (I) and 6-nitrocholest-5-ene (III) with lead (IV) acetate. The products obtained were characterized on the basis of their spectral and chemical studies. The results are summarized in the flow sheet.

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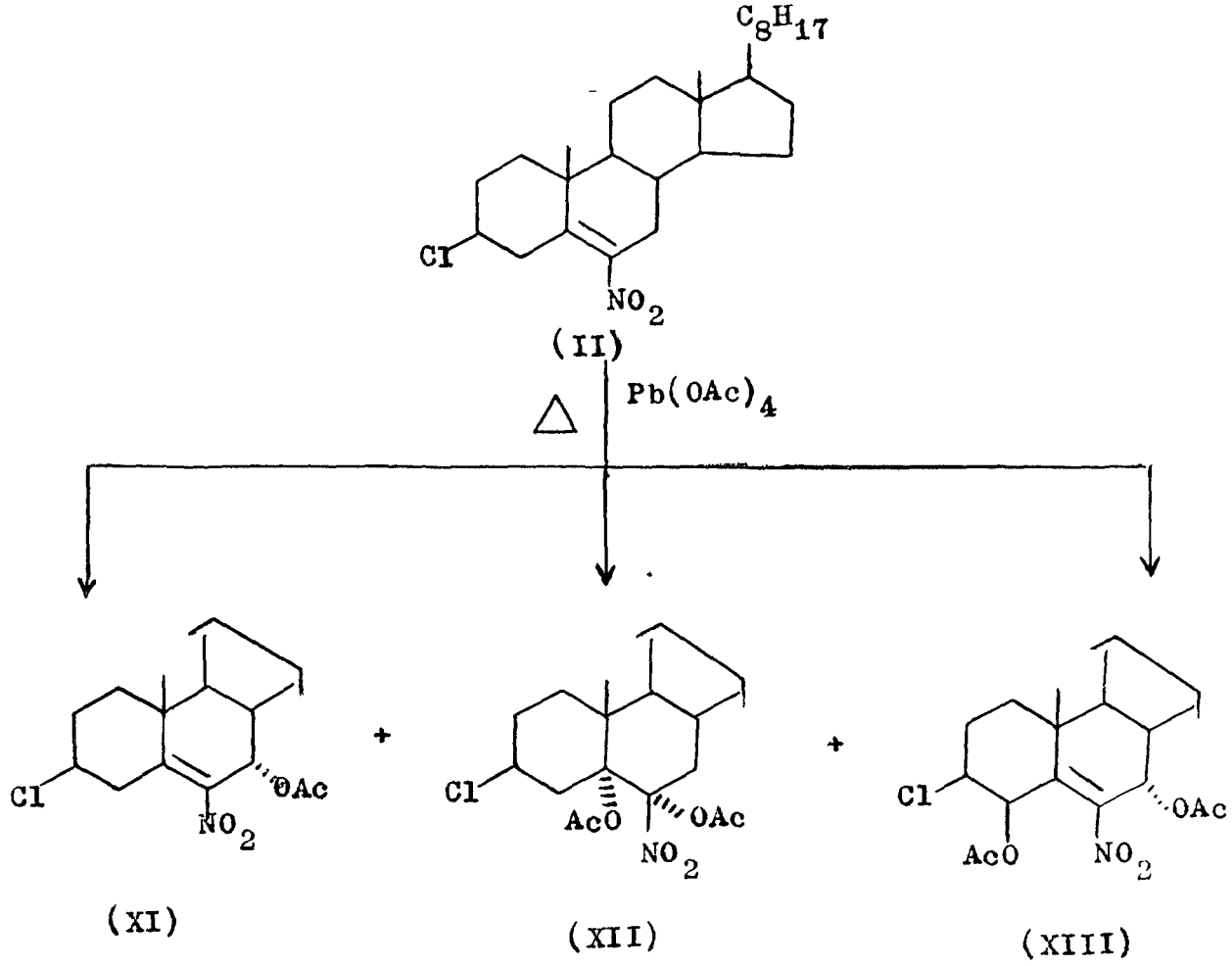
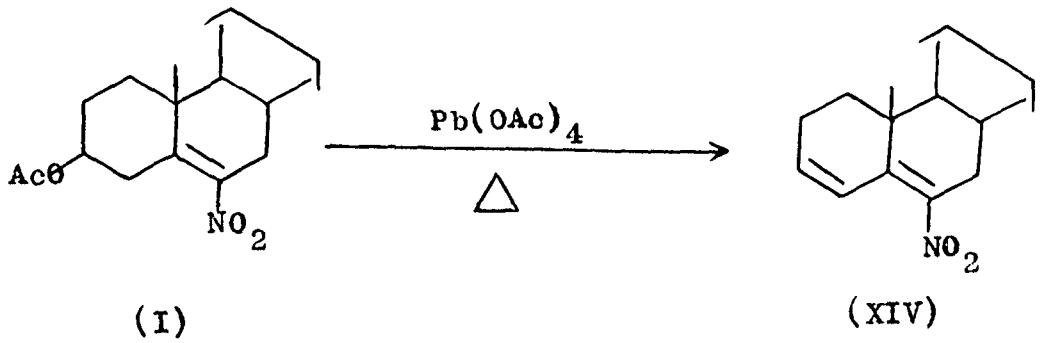
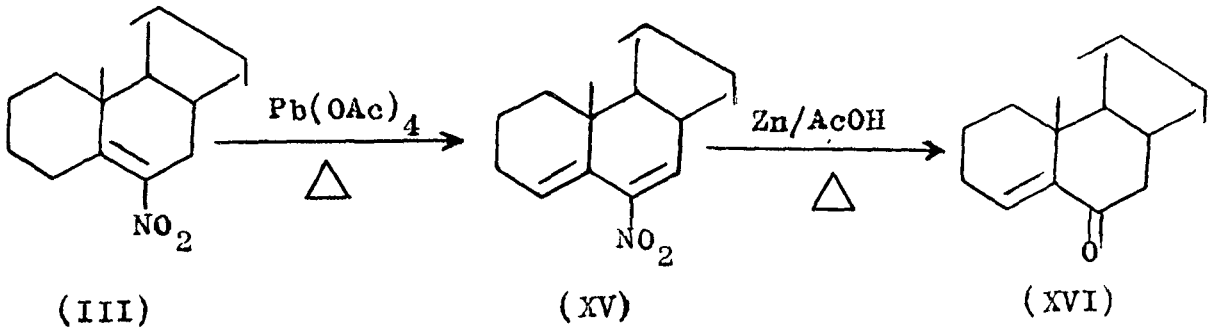
b. Reaction of lead (IV) acetate with steroidal nitroolefins Acta. Chimica. Acad. Sci. (Hung.), 1983, 114, 121.

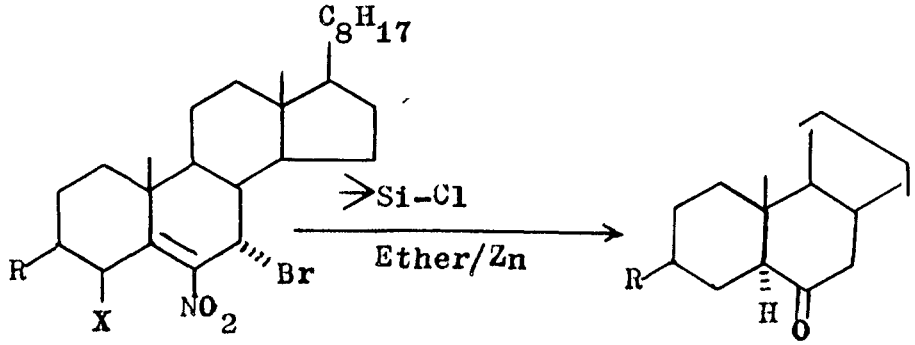

C8H17
Cl
NO2
(II)
Pb(OAc)4
Cl
OAc
NO2
(XI)
+
Cl
AcO
OAc
NO2
(XII)
+
Cl
OAc
AcO
NO2
(XIII)


AcO
NO2
Pb(OAc)4
NO2
(I)
(XIV)


NO2
Pb(OAc)4
NO2
Zn/AcOH
O
(III)
(XV)
(XVI)

(C) Reaction of chlorotrimethylsilane with bromo-6-nitroolefins

Recent publications have highlighted the diverse utility of chlorotrimethylsilane ($ClMe_3Si$) as an important reagent for organic synthesis. This reagent can be used either directly or in combination with suitable metal. The versatile nature of chlorotrimethylsilane in chemical transformations prompted us to carry out the reaction of 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (IV), 3β-chloro-7α-bromo-6-nitrocholest-5-ene (V) and 4β,7α-dibromo-6-nitrocholest-5-ene (VI)[c] with this reagent. Our study showed that chlorotrimethylsilane reduces the olefinic nitro group present in ring 'B' of steroids to ketone and debromination also took place from α- and β-positions.



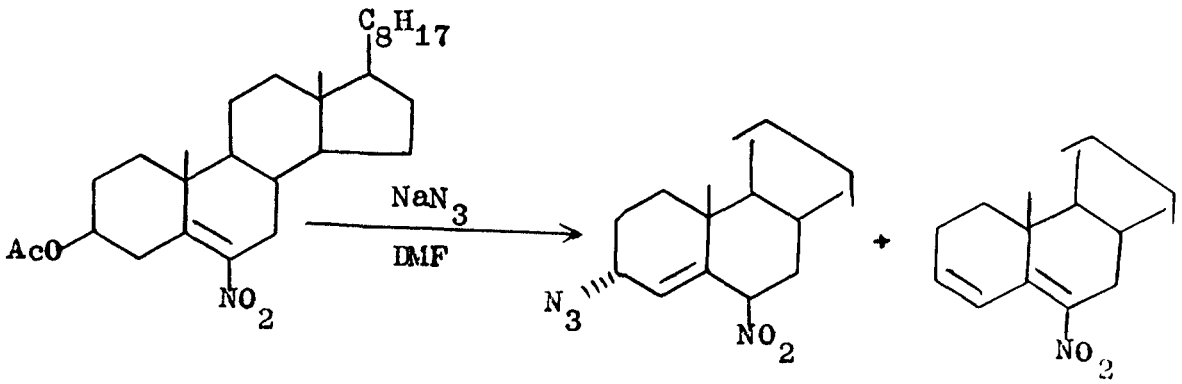
	R	X
(IV)	OAc	H
(V)	Cl	H
(VI)	H	Br

	R
(XVII)	OAc
(XVIII)	Cl
(XIX)	H

c. Application of chlorotrimethylsilane: Reaction of bromo nitroolefins with chlorotrimethylsilane. J. Ind. Chem. Soc. (In press).

(D) Synthesis and Reactions of steroidal conjugated nitroolefins

Conjugated nitroolefins were reported as versatile synthetic intermediates. The present work is concerned with the synthesis of 6-nitrocholesta-3,5-diene (XIV) from 3β-acetoxy-6-nitrocholest-5-ene (I). 3α-Azido-6-nitrocholest-4-ene (XX) was also obtained. The diene (XIV) was converted into 3,6-dinitrocholesta-3,5-diene (XXI)[d] and 3α,4α-epoxy-6-nitrocholest-5-ene (XXIII). The mechanism for the formation of (XXI) has been discussed.



(I) (XX) (XIV)

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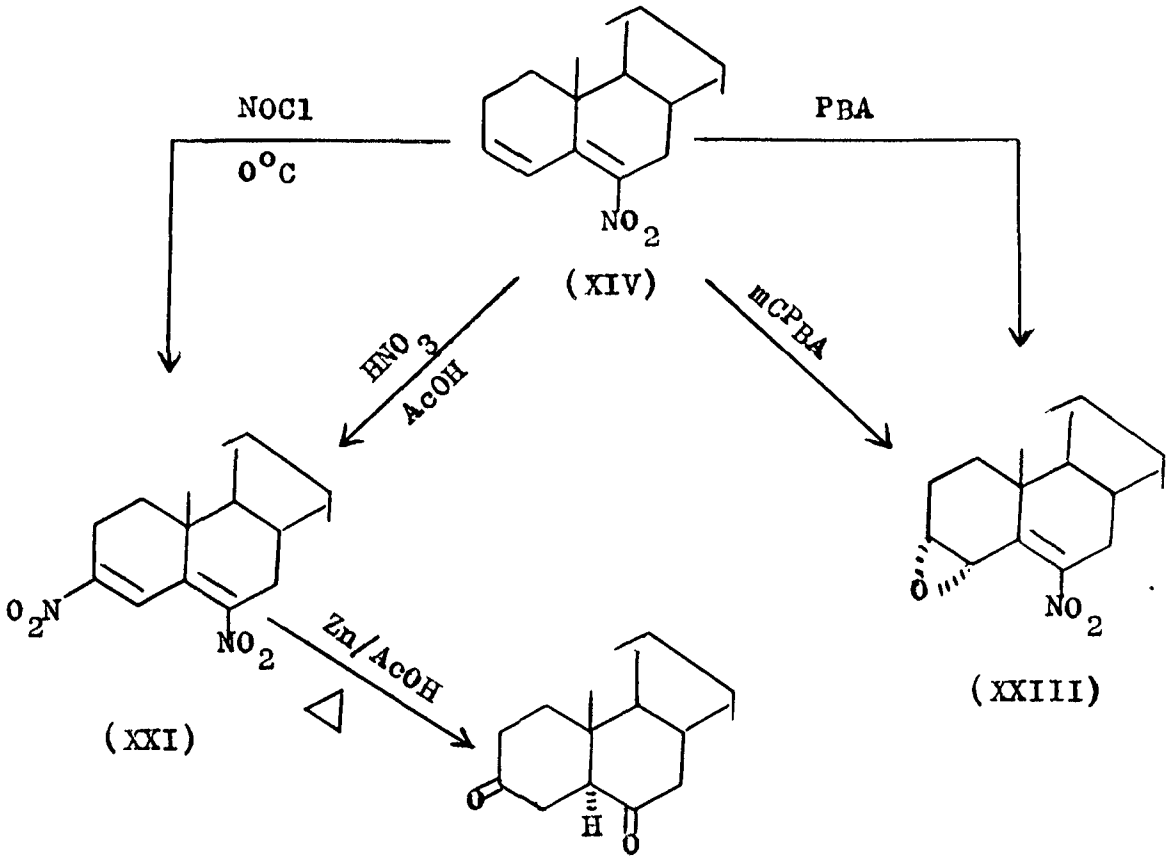
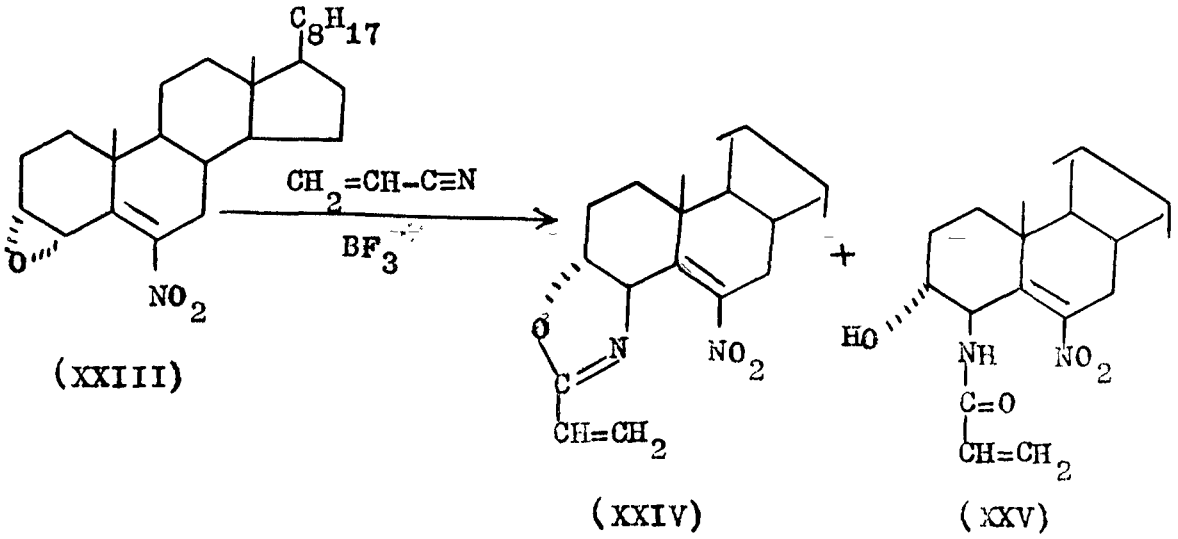
d. Synthesis of steroidal dinitro conjugated olefins J. Chem. Research(s); 1983, 255.



(E) Synthesis of steroidal oxazoline

In the recent past, much attention has been paid towards the formation of oxazolines because of the significant biological properties associated with a number of oxazolines and their use as potential drugs. As a result of this realization attempt was made in present study to synthesize the steroidal oxazoline. The epoxide (XXIII) on treatment with acrylonitrile (BF_3-etherate catalyst) gave oxazoline (XXIV) and amido alcohol (XXV).

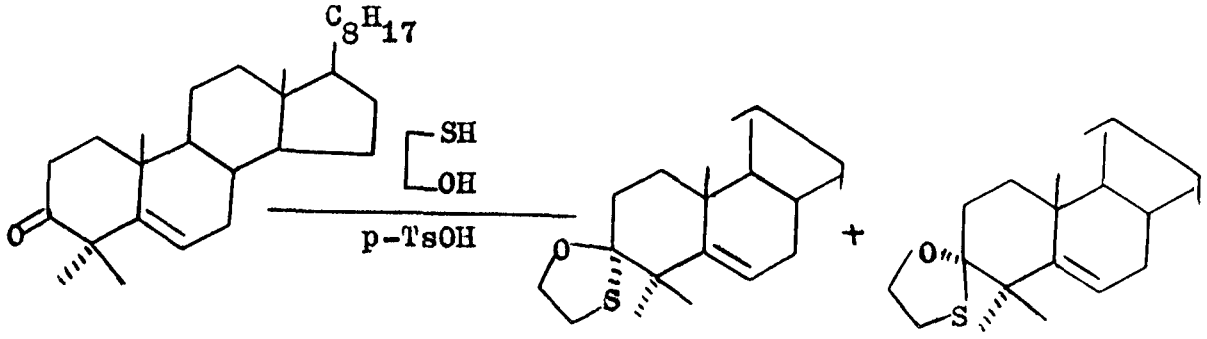


Part two

Synthesis of steroidal oxathiolanes

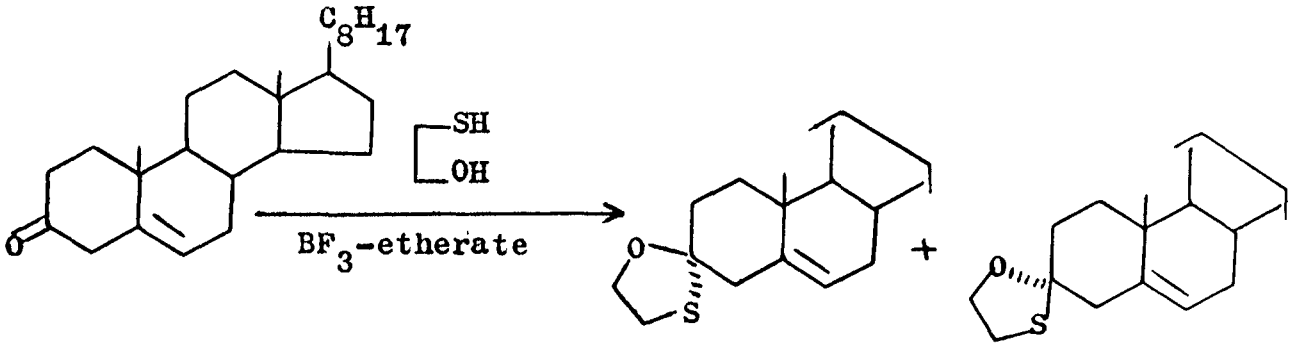
A number of steroidal oxathiolanes were synthesized in our laboratories. Further attempts were made in present study to synthesize the steroidal oxathiolanes derived from hitherto unexplored steroidal ketones such as (XXVI), (XXVII) and (XXVIII).[e] The ketone (XXVI) on treatment with β-mercaptoethanol in the presence of p-toluenesulphonic acid gave isomeric oxathiolanes (XXIX) and (XXX).

e. Synthesis of steroidal oxathiolanes
J. Prakt. Chem; 1982, 324(1), 155.

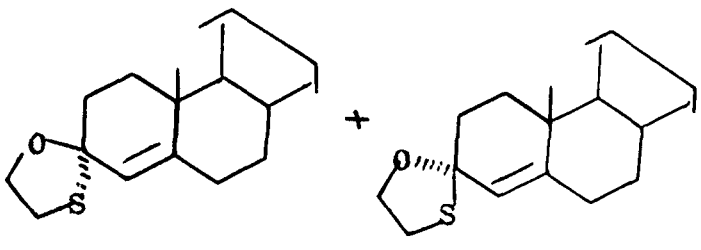


(XXVI) (XXIX) (XXX)

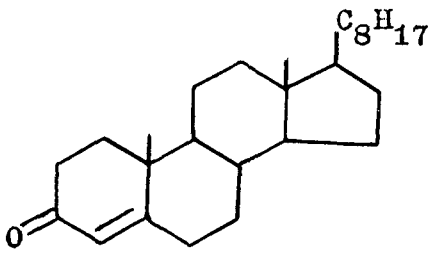
When the ketones (XXVII) and (XXVIII) were subjected to react with same reagent (β-mercaptoethanol) in presence of BF_3-etherate, they gave isomeric oxathiolanes (XXXI), (XXXII), (XXXIII) and (XXXIV). The structure of oxathiolanes with special reference to configuration of oxathiolane ring was established with the help of NMR spectra.



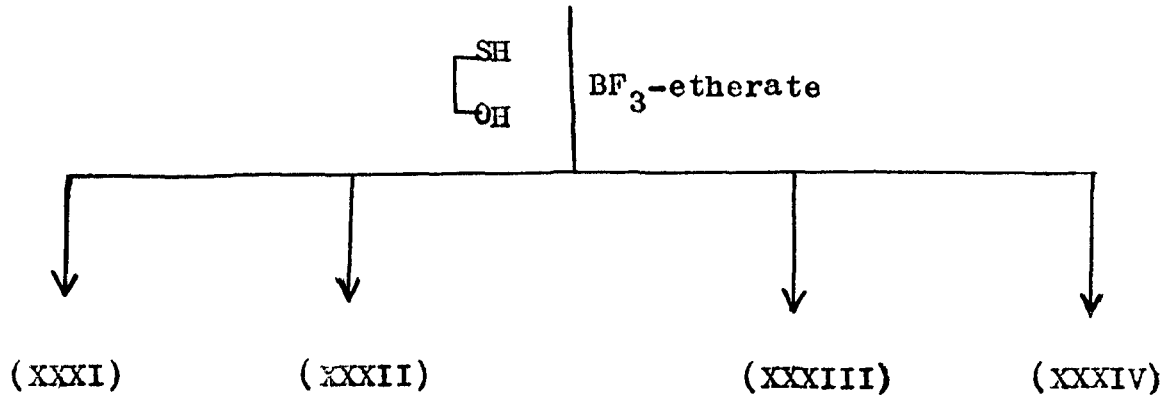
(XXVII) (XXXI) (XXXII)



(XXXIII) (XXXIV)



(XXVIII)



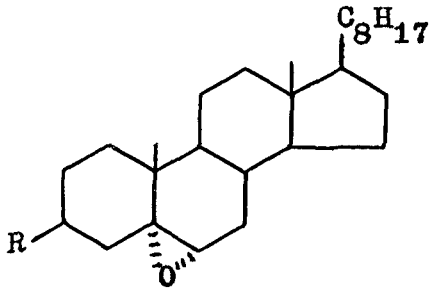
(XXXI) (XXXII) (XXXIII) (XXXIV)

Part three

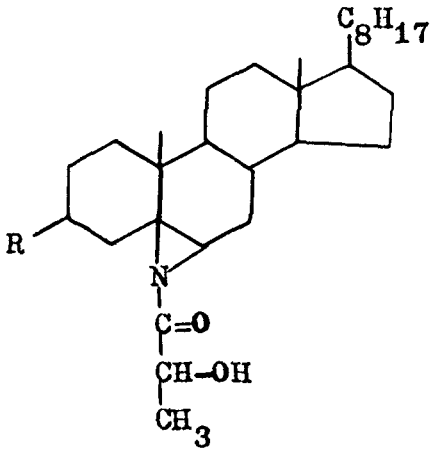
Synthesis of steroidal aziridines

A number of papers dealing with the synthesis of aziridines have appeared in recent years and few of them are claimed to possess the biological activity. This prompted us to synthesize new steroidal aziridines (XXXVIII), (XXXIX),

(XL) and (XLI)[f] from 5,6α-epoxy-5α-cholestane (XXXV), 3β-acetoxy-5,6α-epoxy-5α-cholestane (XXXVI) and 3β-chloro-5,6α-epoxy-5α-cholestane(XXXVII) respectively. The structure of steroidal aziridines obtained was confirmed on the basis of spectral studies.



	R
(XXXV)	H
(XXXVI)	OAc
(XXXVII)	Cl



	R
(XXXVIII)	H
(XXXIX)	OH
(XL)	OAc
(XLI)	Cl

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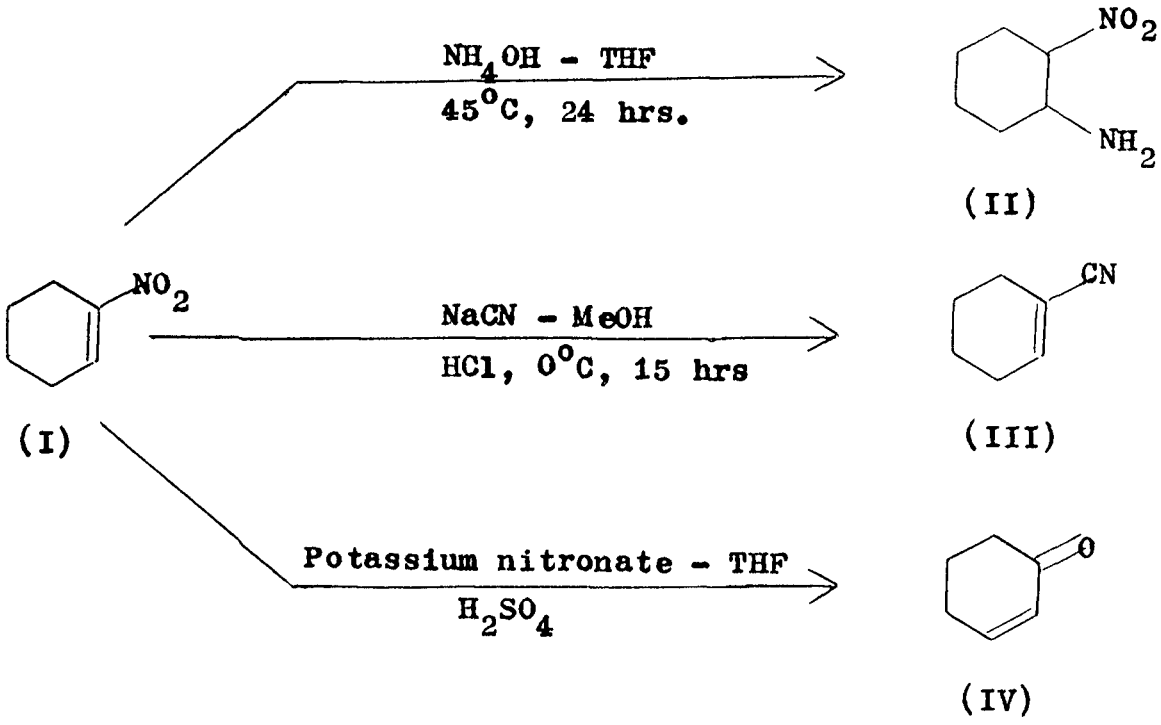
f. Synthesis of steroidal aziridines
Acta. Chimica. Acad. Sci. (Hung.) (In press).

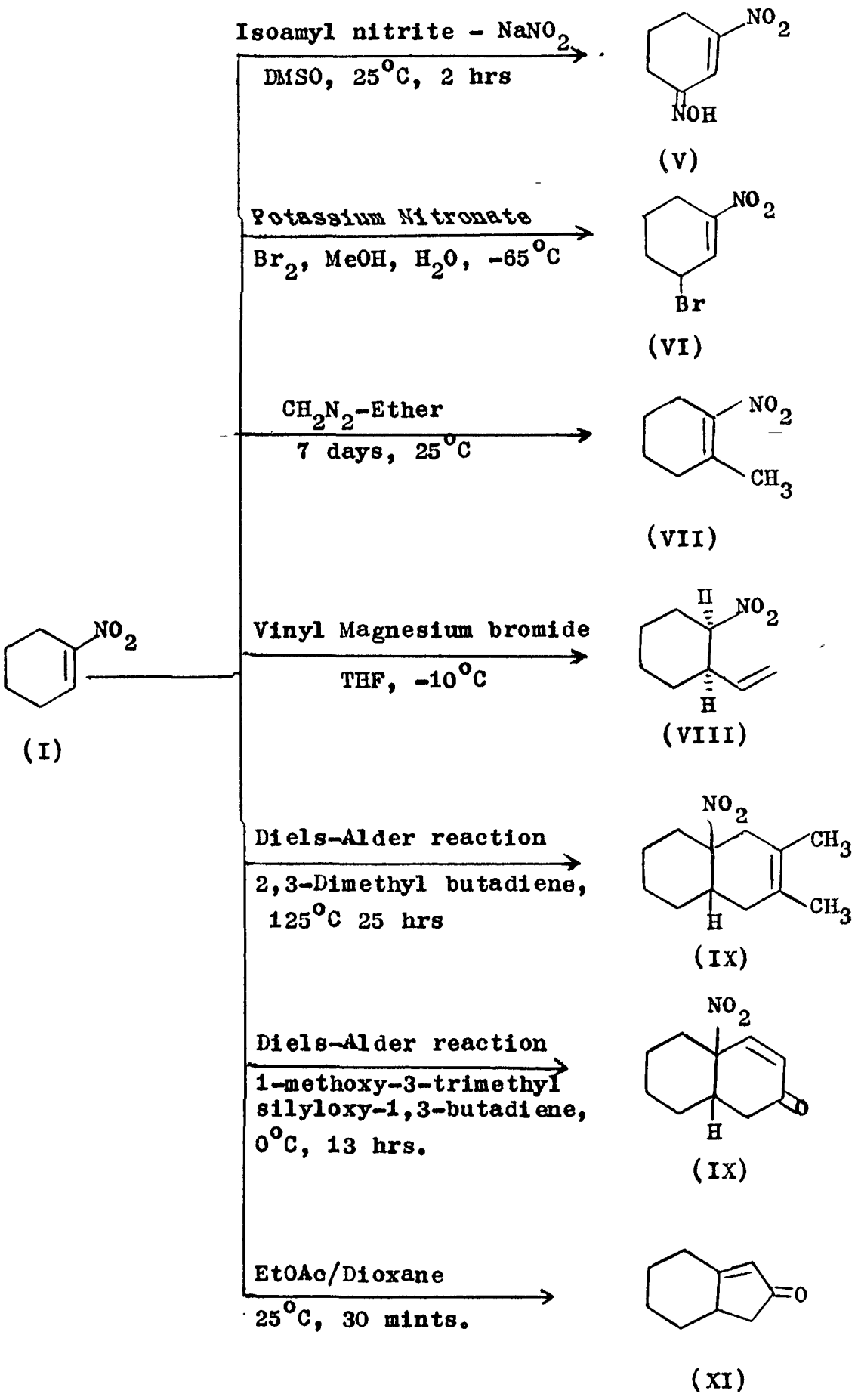
PART ONE

Reactions of Nitro Steroids

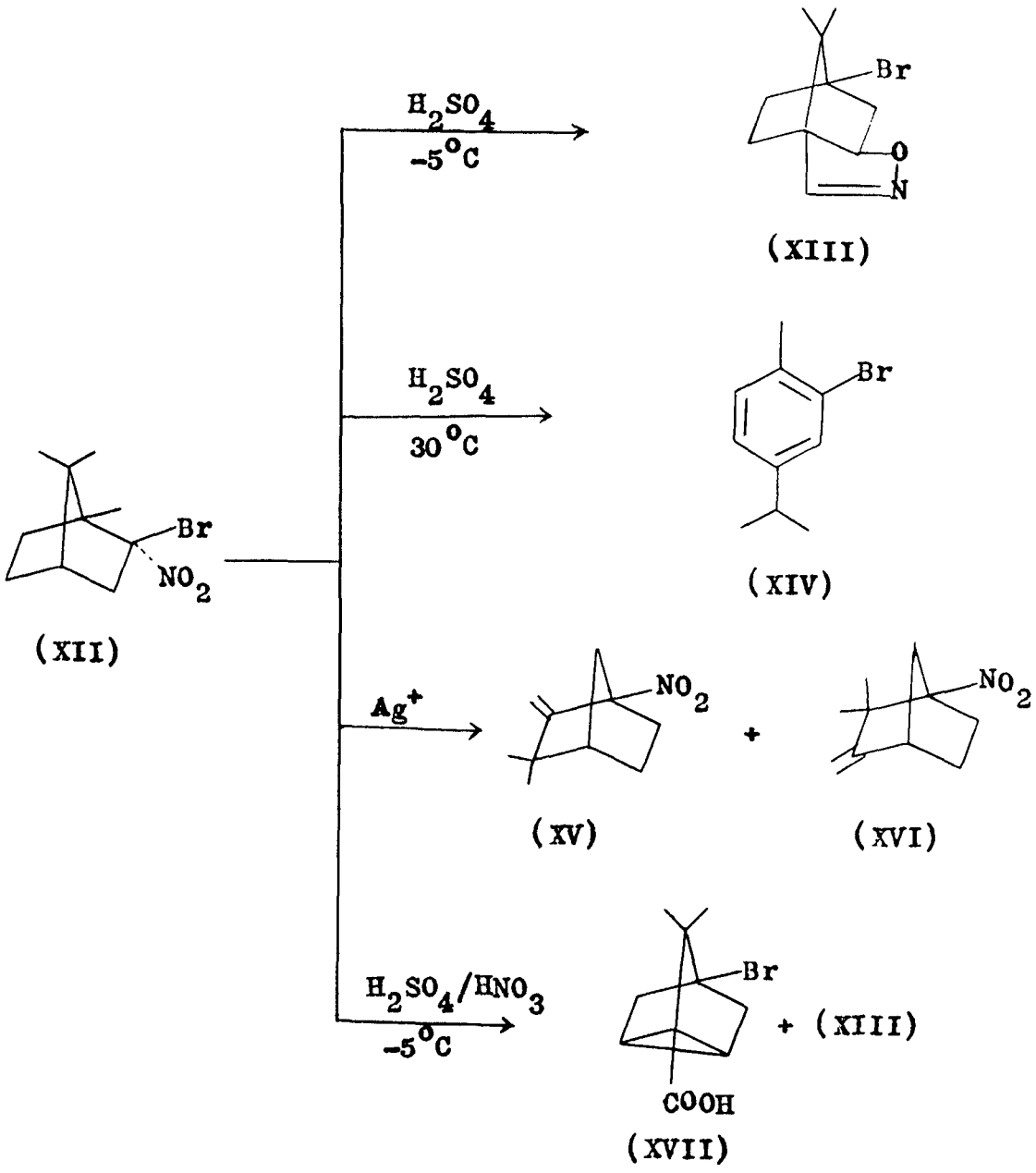
Theoretical

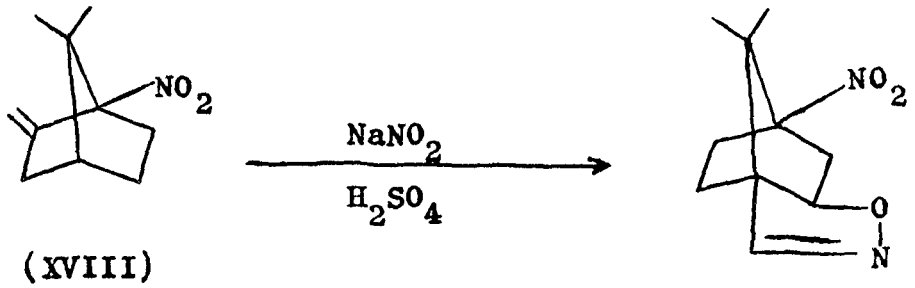
Conjugated cyclic nitro-olefins are potentially versatile and unique as synthetic intermediates. In the recent past, much efforts are being made by chemists to synthesize a number of organic compounds through these intermediates. This chapter envisage the coverage of literature for the reactions of nitro-compounds. Corey and Treicher[1] suggested that the versatility of cyclo olefinic nitro unit in synthesis is noteworthy because of its complementary relationship to other functional groups. They reported the reactions of 1-nitrocyclohexane (1) with various reagents which illustrate the broad range of applications of olefinic nitro group.




Isoamyl nitrite - NaNO2
DMSO, 25°C, 2 hrs
NO2
NOH
(V)
Potassium Nitronate
Br2, MeOH, H2O, -65°C
NO2
Br
(VI)
CH2N2-Ether
7 days, 25°C
NO2
CH3
(VII)
NO2
(I)
Vinyl Magnesium bromide
THF, -10°C
NO2
(VIII)
Diels-Alder reaction
2,3-Dimethyl butadiene,
125°C 25 hrs
NO2
CH3
CH3
(IX)
Diels-Alder reaction
1-methoxy-3-trimethyl
silyloxy-1,3-butadiene,
0°C, 13 hrs.
NO2
(IX)
EtOAc/Dioxane
25°C, 30 mints.
(XI)

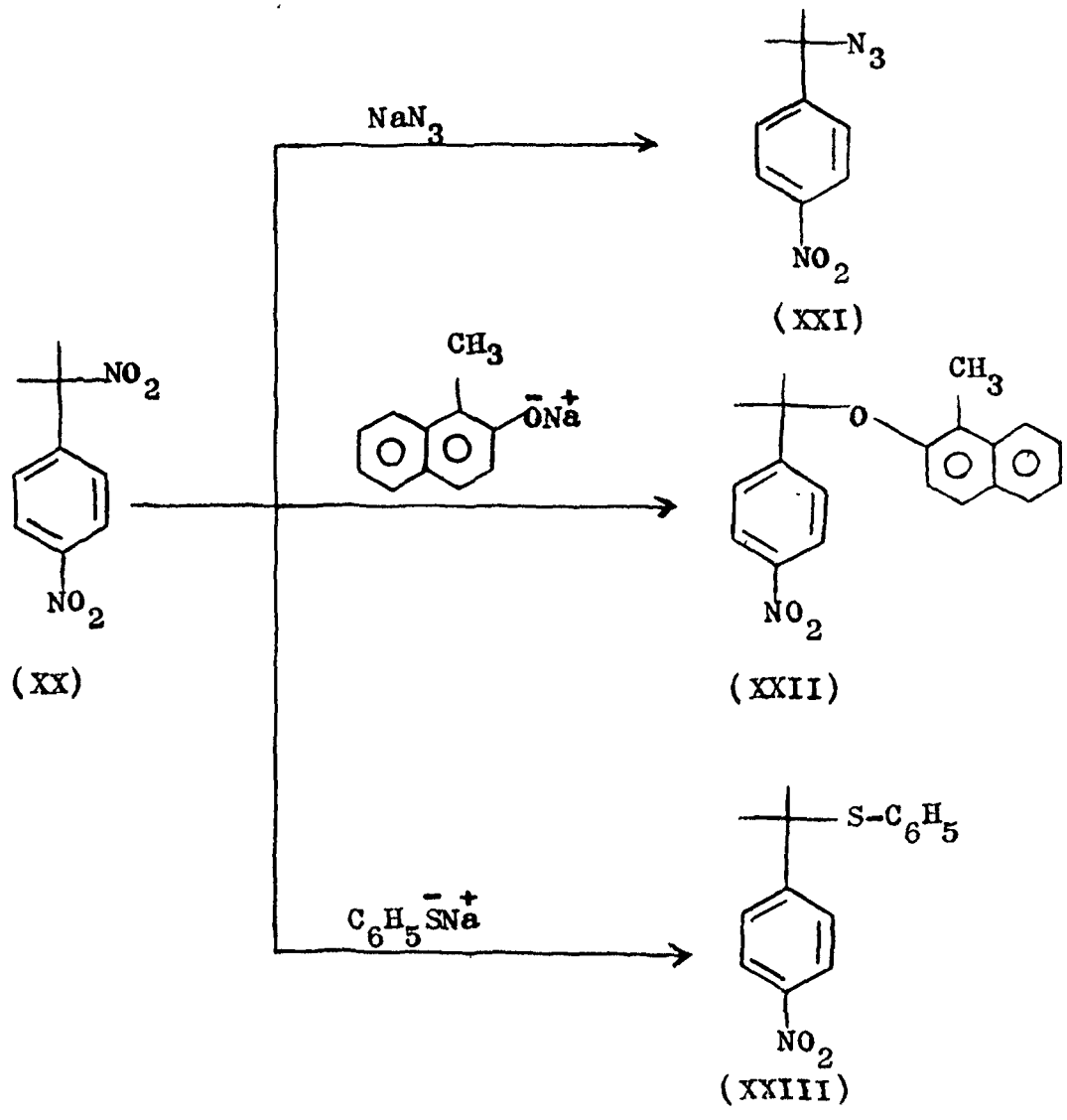
Ranganathan and Raman[2] carried out the reaction of bromonitrocamphane (XII) and ω -nitrocamphene (XVIII) to obtain anhydrobromonitrocamphane (XIII), 2-bromo-p-cymene (XIV), 4-nitrocamphene (XV), 1-nitrocamphene (XVI), bromotricylene acid (XVII) and 4-nitroisoxazoline (XIX) respectively under different reaction conditions.

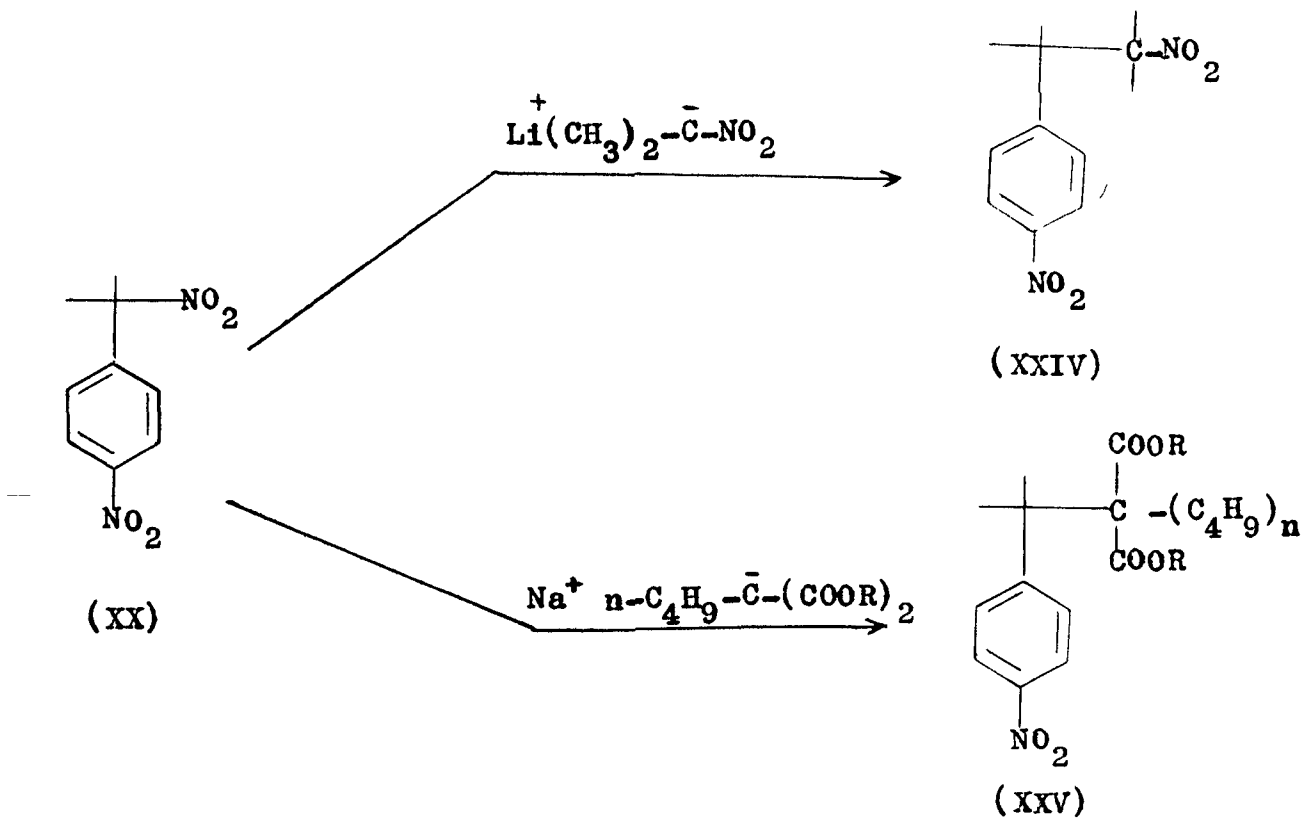




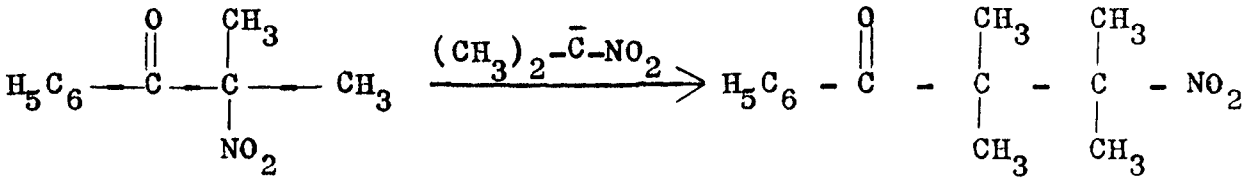
(XVIII) (XIX)

Kornblum et al.[3] reported that the reactions of ∝ -p-dinitrocumene (XX) were noteworthy because they involved substitution at a tertiary carbon and the displacement of a nitro group from a saturated carbon atom.

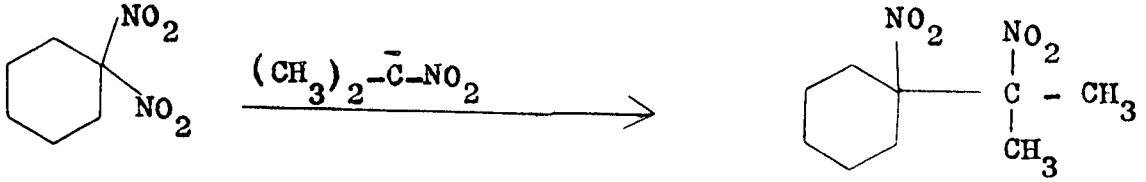




Kornblum et al.[4] also reported the first example of the displacement of α-nitro group from α-nitroketone (XXVI) and α,α-dinitro compounds (XXVII) by nitroalkyl anions.

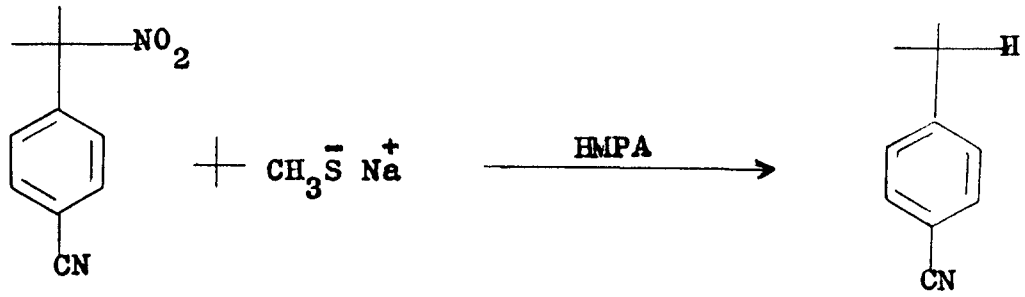


(XXVI)

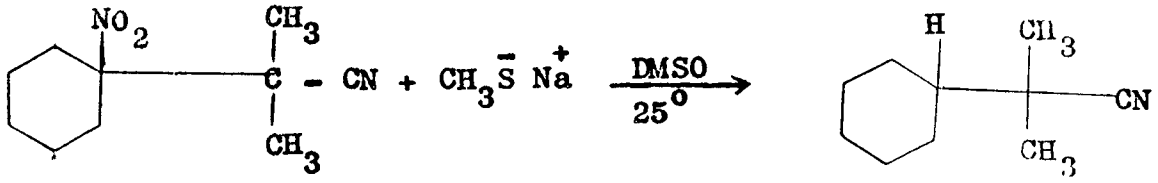


(XXVII)

It has been found[5,6] that hydrogen replaces the nitro group from the compound such as (XXVIII) and (XXIX) on treatment with sodium salt of methyl mercaptan.

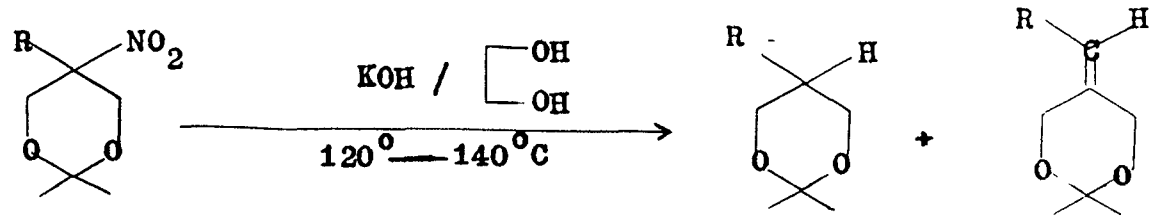


(XXVIII)



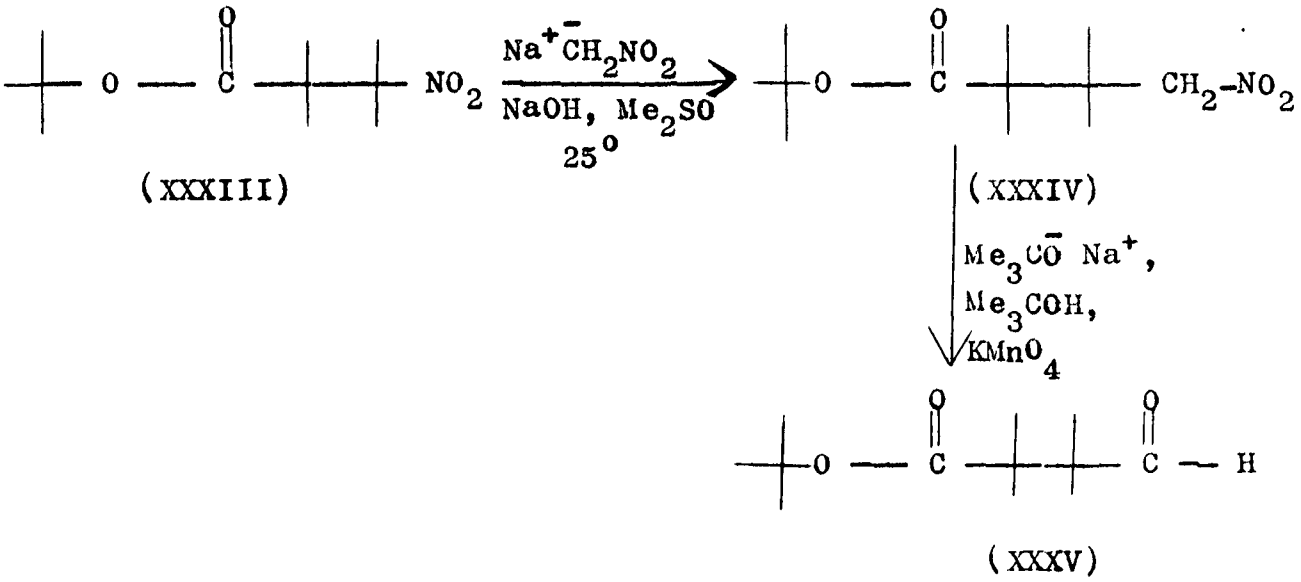
(XXIX)

Krasuska et al.[7] reported the replacement of tertiary nitro group in 5-nitro-1,3-dioxane (XXX) by hydrogen atom to yield 1,3-dioxanes (XXXI) and (XXXII).



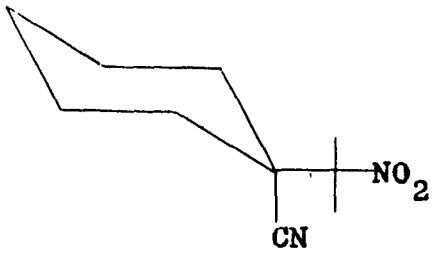
(XXX) (XXXI) (XXXII)

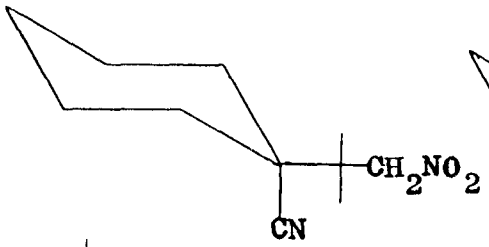
Kornblum et al.[8] reported the replacement of nitro group by CH_2NO_2 and they converted the primary nitro compounds to aldehydes by potassium permanganate oxidation at 0°C.

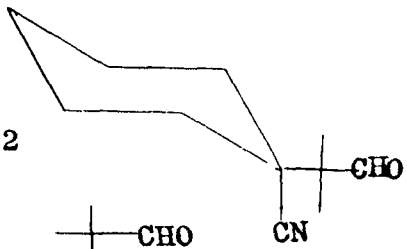


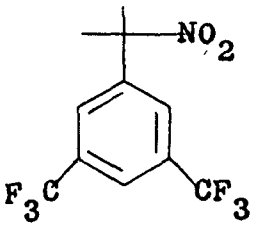
Replacement of $3^{o}NO_2$ by CH_2NO_2 and conversion of 1^{o} nitro compounds to aldehydes

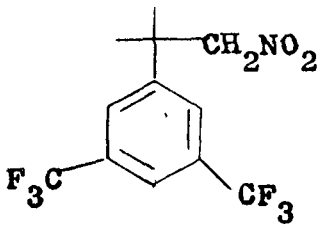
3^{o}-NO_2 groups	1^{o}-Nitro compounds	Aldehydes

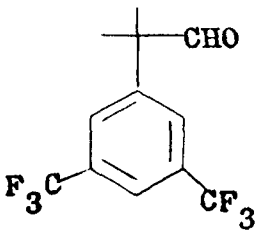


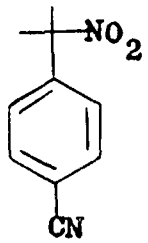


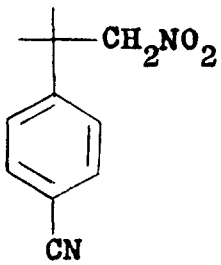


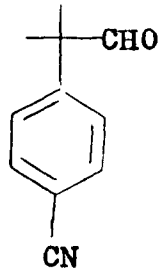


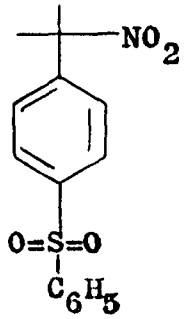


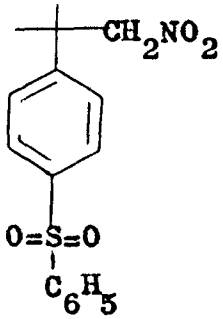


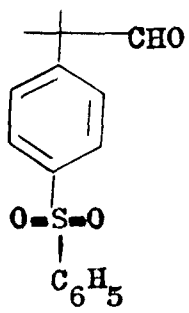




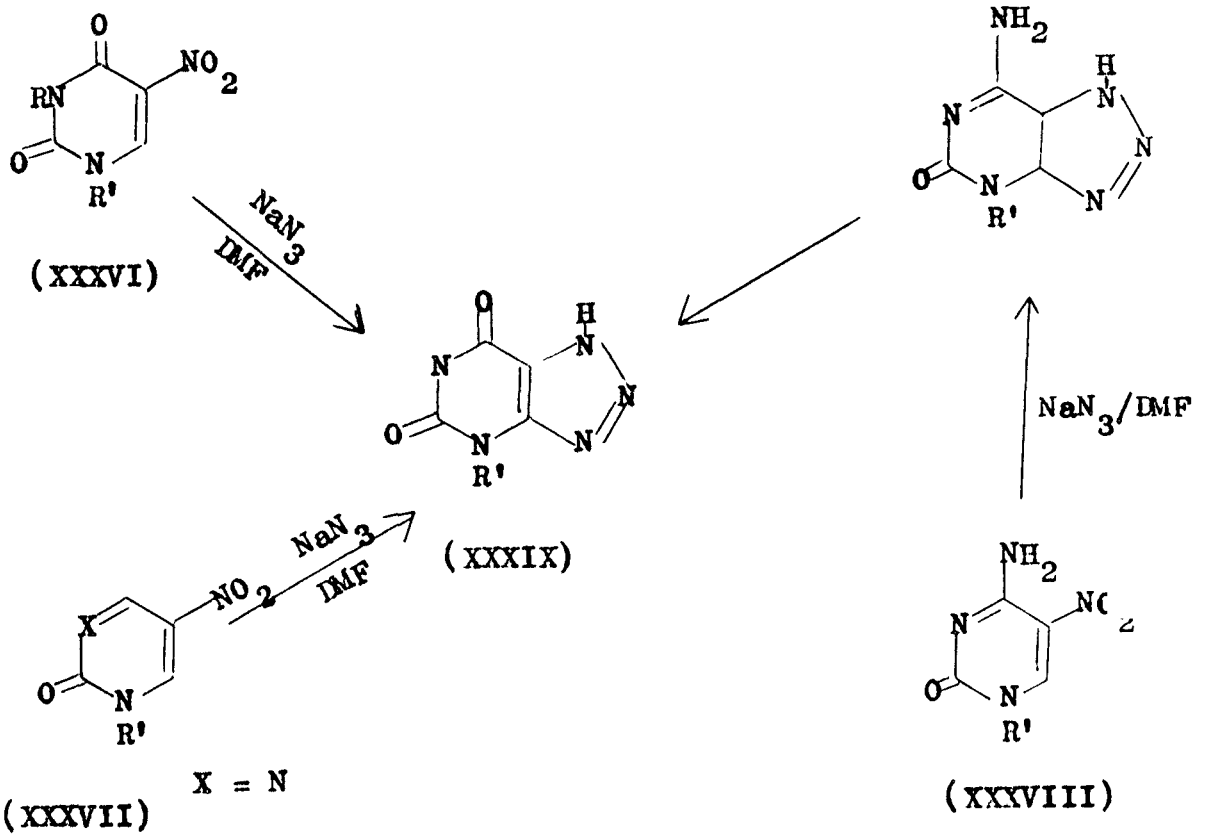






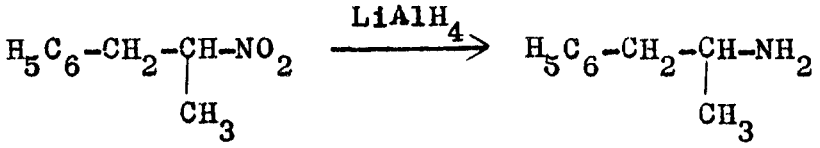


Ulrich and Fox[9] reported that the treatment of 5-nitropyrimidines (XXXVI, XXXVII) and 5-nitrocytidine (XXXVIII) with sodium azide leads to a novel, one step synthesis of 2-oxo-8-azapurine (XXXIX).



(XXXVI) (XXXIX) (XXXVIII) (XXXVII)

Gilsdrof et al.[10] reported lithium aluminium hydride reduction of 1-phenyl-2-nitropropane (XXXIX) followed by hydrolysis with an aqueous sodium or potassium tartrate solution to give β-phenylisopropylamine (XL).

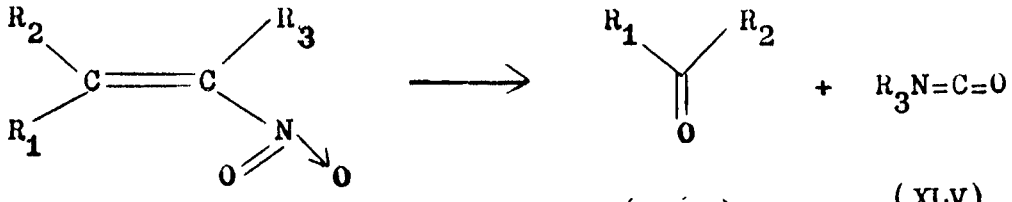


(XXXIX) (XL)

Schlesinger et al.[11,12] reported the reduction of α,β-unsaturated nitro derivative (XLI) to yield (XLII).

(XLI) (XLII)

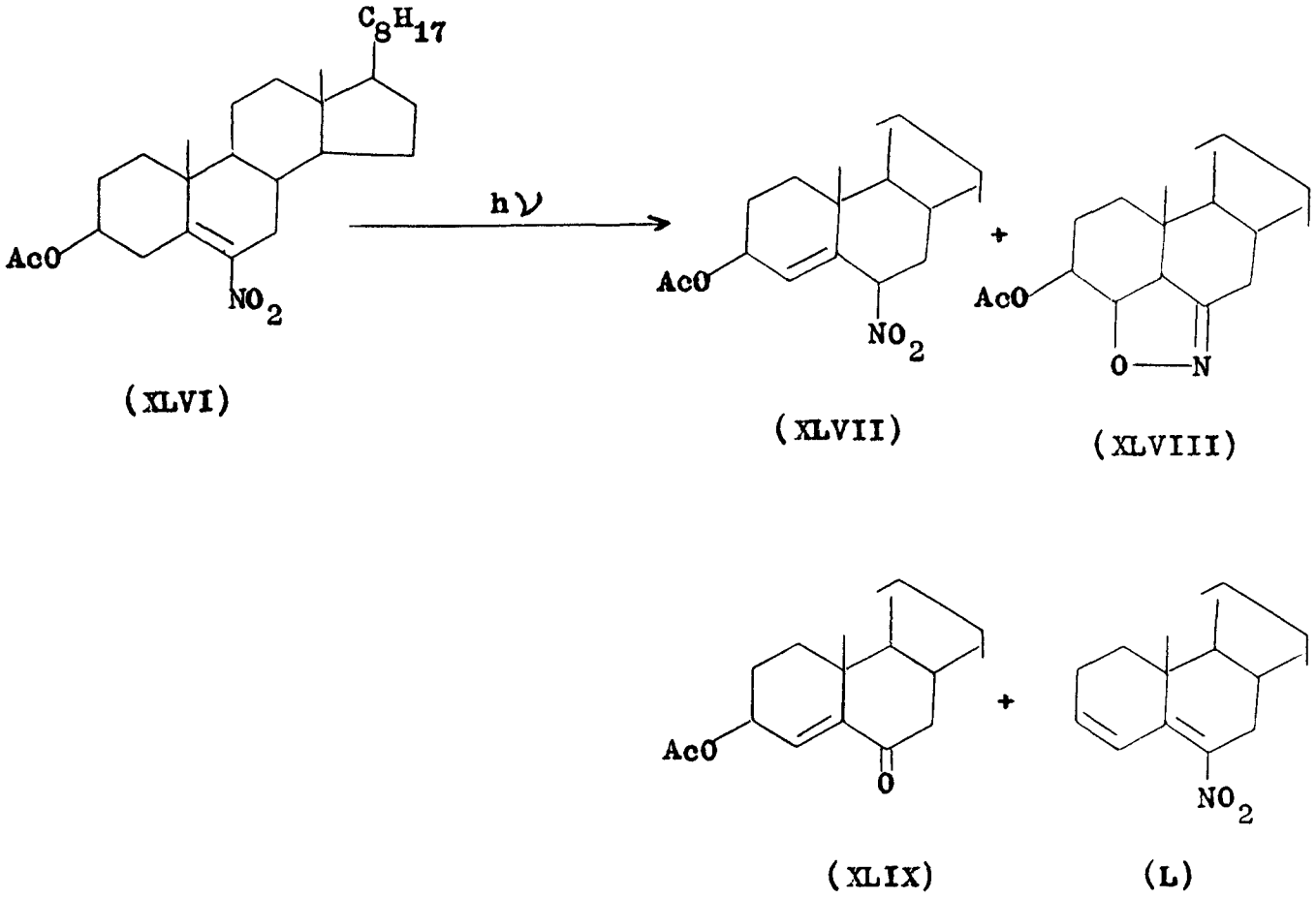
Kinstle and Stam[13] reported that α,β-unsaturated nitro compound (XLIII) on photochemical rearrangement provided carbonyl compound (XLIV) and nitrileoxide (XLV) as products.



(XLIII) (XLIV) (XLV)

It has been found that[14,15] the irradiation of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) in hexane gave 6β-nitro-

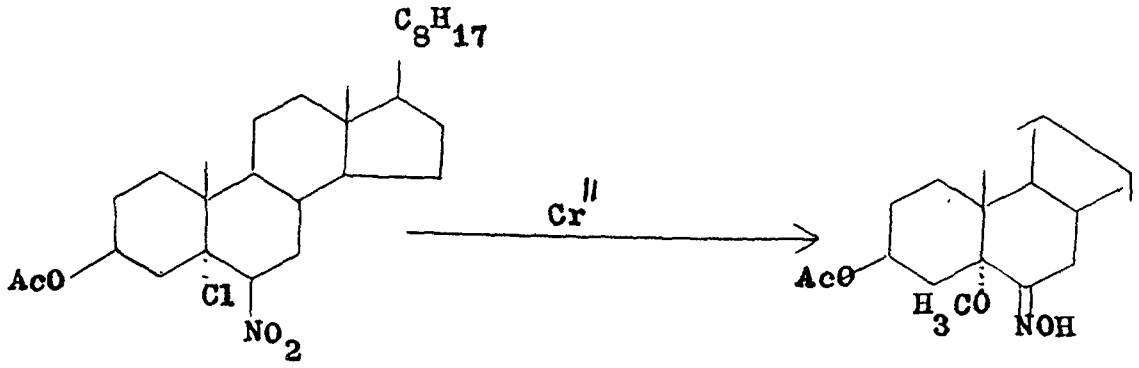
cholest-4-en—3β-yl-acetate (XLVII) along with other products (XLVIII), (XLIX) and (L).



(XLVI) (XLVII) (XLVIII)

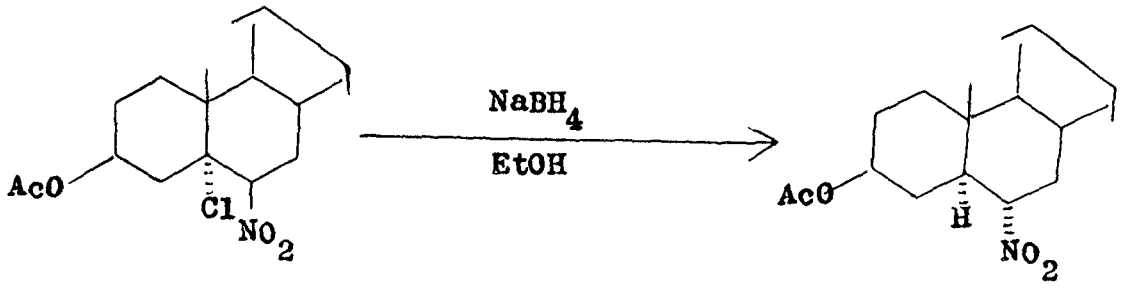
(XLIX) (L)

Hassner and Heathcock[16] treated 3β-acetoxy-5α-chloro-6-nitrocholestane (LI) with chromous chloride in methanolic hydrochloric acid to obtain 3β-acetoxy-5α-methoxy-6-oximino-cholestane (LII).

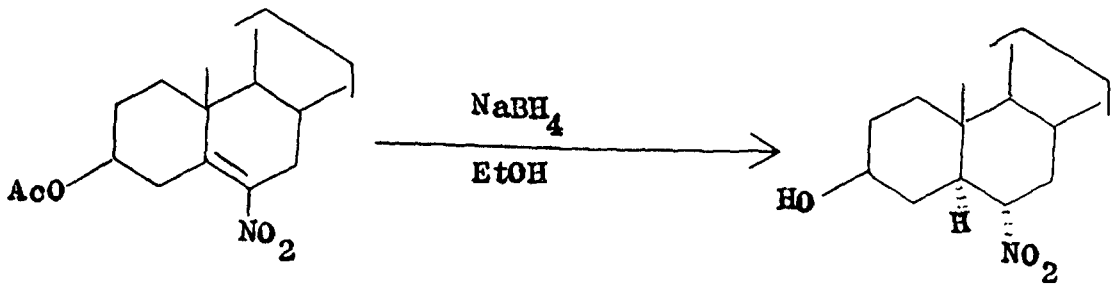


(LI) (LII)

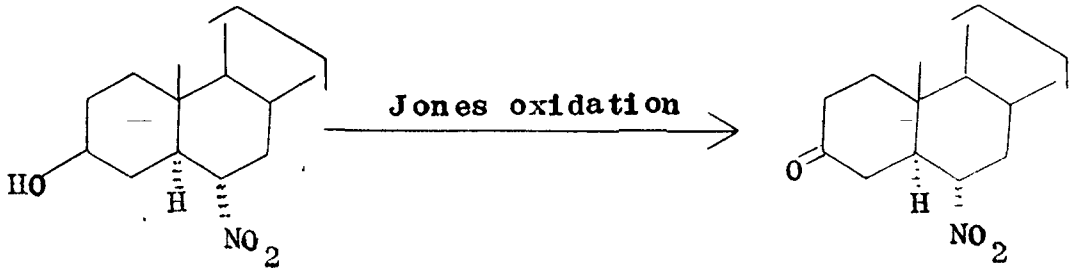
The reduction of 5α-chloro-6β-nitrosteroids (LI) and (XLVI) with sodium borohydride in ethanol afforded 6α-nitro-5α-steroids (LIII) and (LIV) respectively. Jones oxidation of (LIV) gave 6α-nitrocholestan-3-one (LV).



(LI) (LIII)

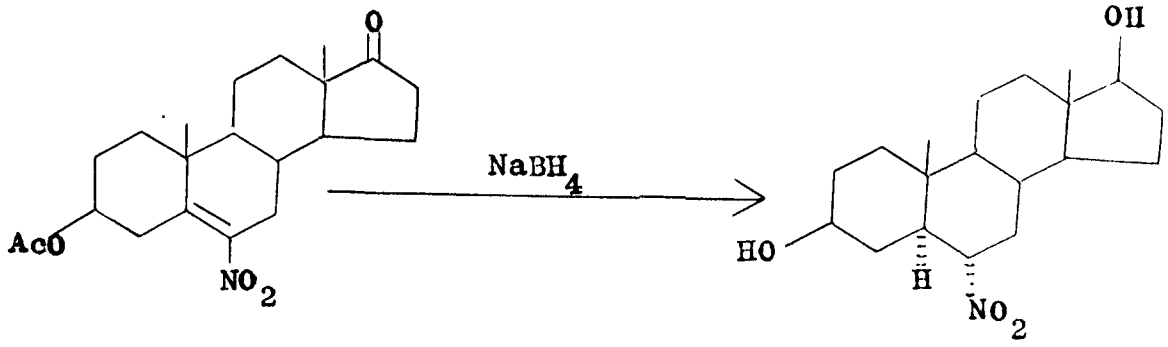


(XLVI) (LIV)



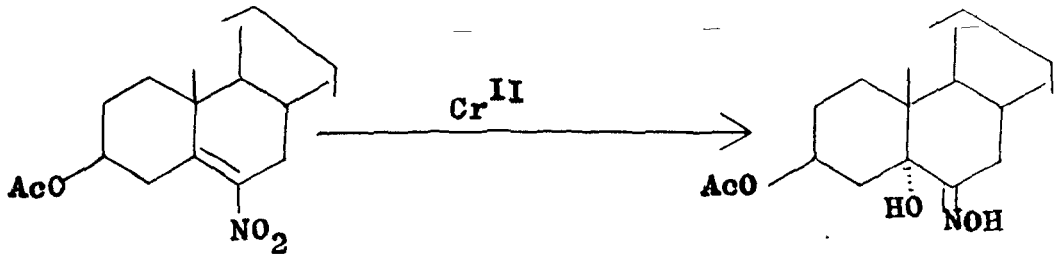
(LIV) (LV)

3β-Acetoxy-6-nitroandrosten-17-one (LVI) was reduced by sodium borohydride to 6∝-nitroandrostan-3β,17β-diol (LVII).[16]



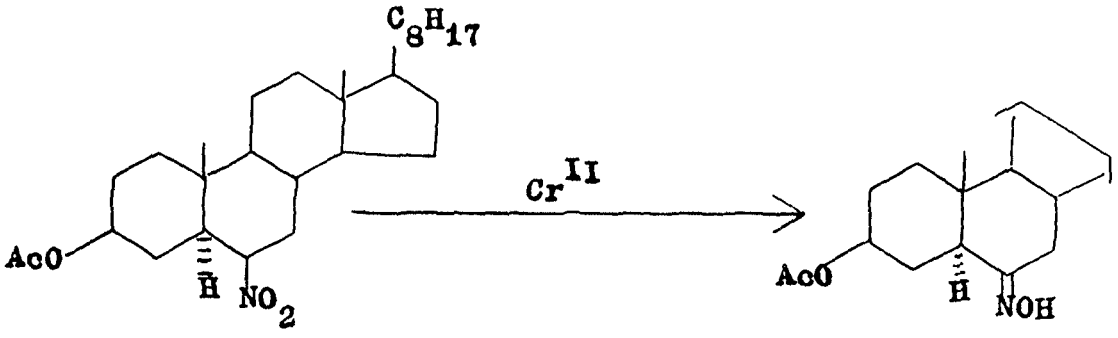
(LVI) (LVII)

Hanson and Premuzic[17] treated 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with chromous chloride for three hours to obtain oxime (LVIIIa)

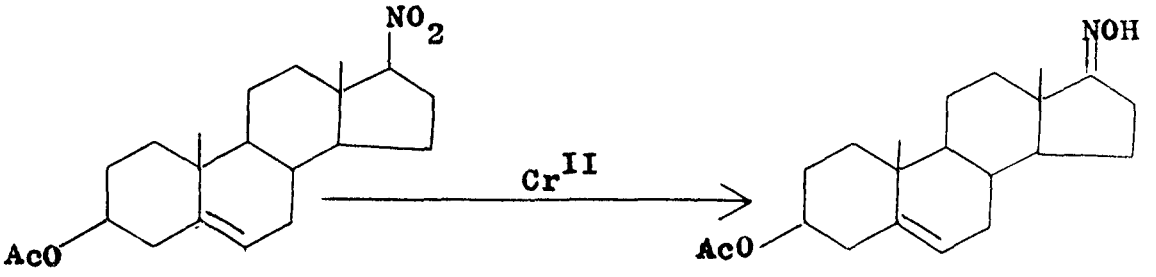


(XLVI) (LVIIIa)

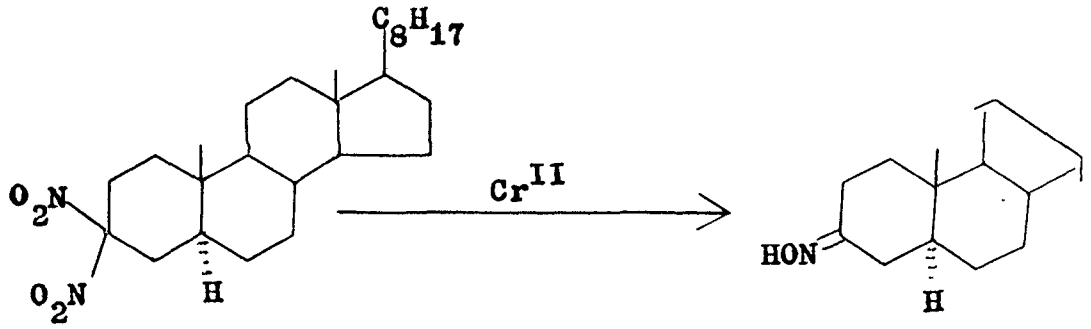
Hanson and Organ[18] carried out the reduction of 3β-acetoxy-6β-nitro-5α-cholestane (LIX) under nitrogen with acidic chromium (II) chloride to give 3β-acetoxy-6-hydroxylamino-5α-cholestane (LX). 3β-Acetoxy 17β-nitrocholest-5-ene (LXI) under similar reaction conditions provided oxime (LXII) whereas 3,3-dinitro-5α-cholestane (LXIII) afforded oxime (LXIV).[19]



(LIX) (LX)

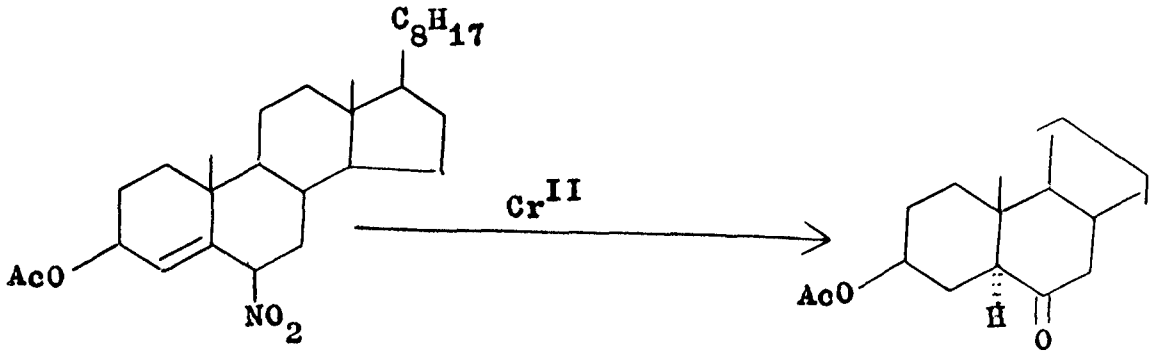


(LXI) (LXII)

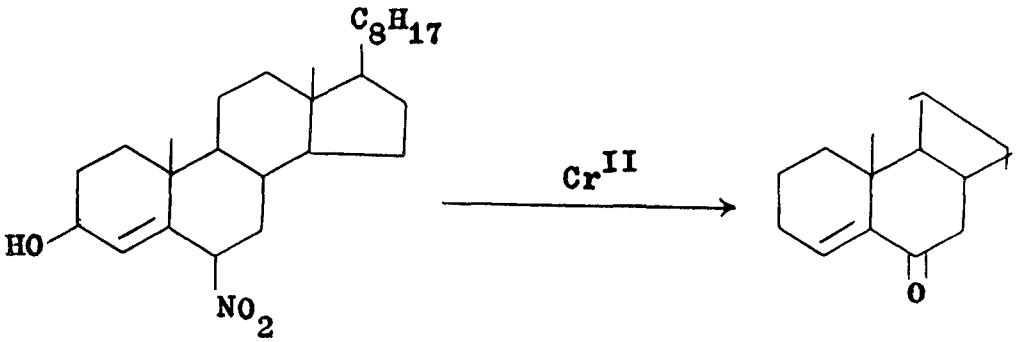


(LXIII) (LXIV)

In contrast, α,β-unsaturated nitro steroid such as 3β-acetoxy-6β-nitrocholest-4-ene (XLVII) afforded the 6-ketone (LXV) rather than oxime. Reduction of the corresponding 3β-alcohol (LXVI) gave cholest-4-en-6-one (LXVII).[20]

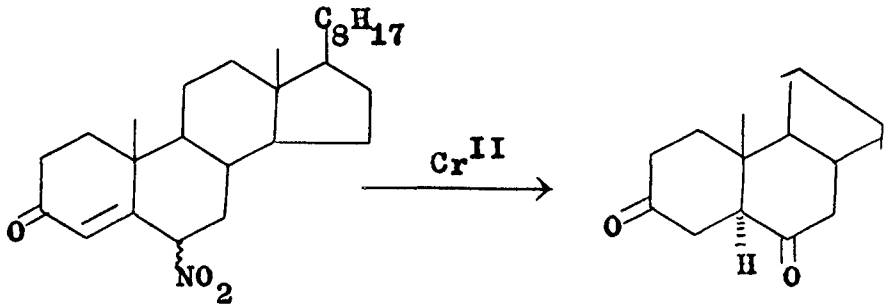


(XLVII) (LXV)



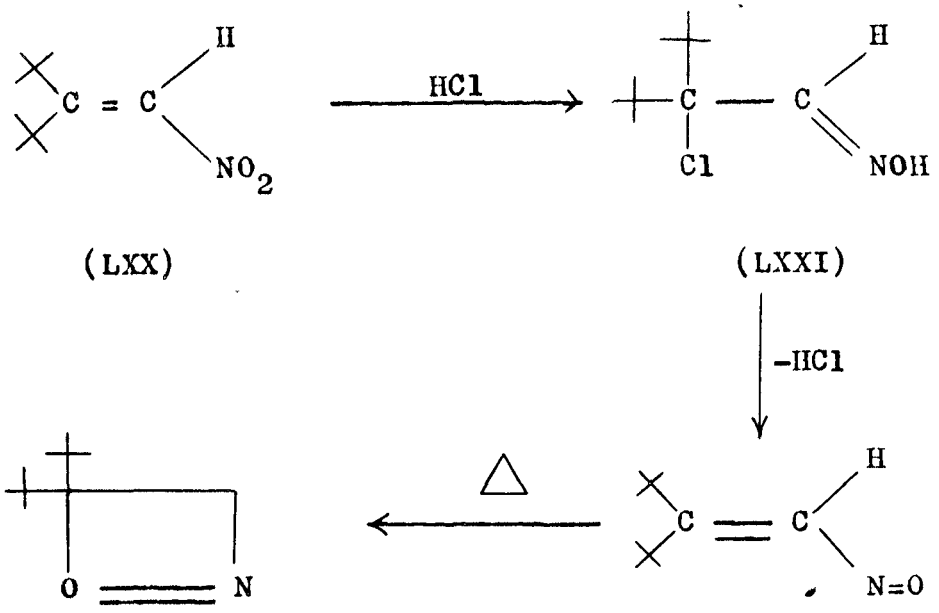
(LXVI) (LXVII)

Reduction of 6α- and 6β-nitrocholest-4-en-3-one (LXVIII) gave 5α-cholestan-3,6-dione (LXIX).



(LXVIII) (LXIX)

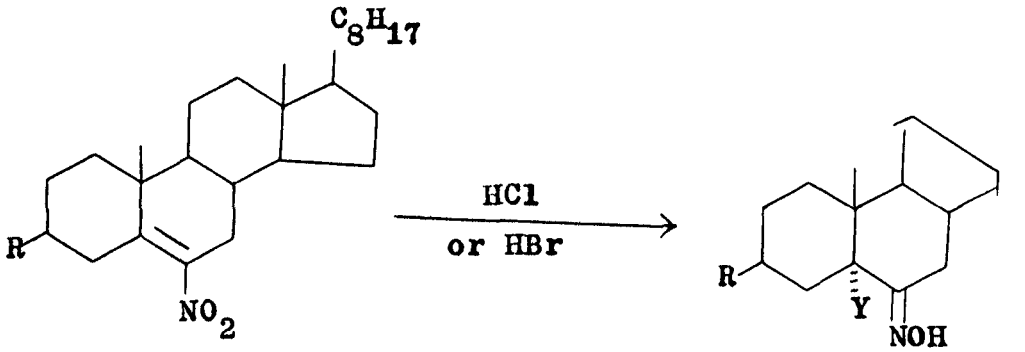
α-Chlorooxime (LXXI) prepared by the nitroalkene (LXX)[21,22,23] was converted into 2-tertiary butyl 3,3-dimethyl 1-nitroso-1-butene (LXXII) which on heating to 220° furnished 4,4-ditertiary butyl-4H-1,2-oxazete (LXXIII).



(LXX) (LXXI)

(LXXIII) (LXXII)

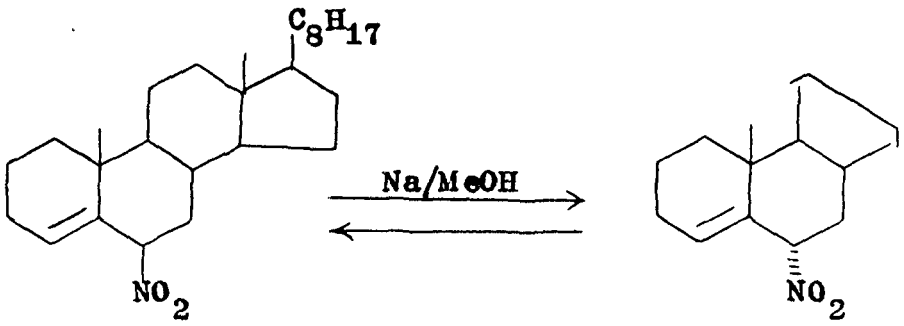
Yoshihisa et al.[24] found that the treatment of 6-nitro-cholest-5-enes (XLVI, LXXIV, LXXV) with dry hydrogen chloride or bromide produces hitherto unaccessible 5α-chloro or 5α-bromo-6-oximino-5α-cholestanes (LXXVI-LXXIX) in high yield.



	R
(XLVI)	OAc
(LXXIV)	Cl
(LXXV)	H

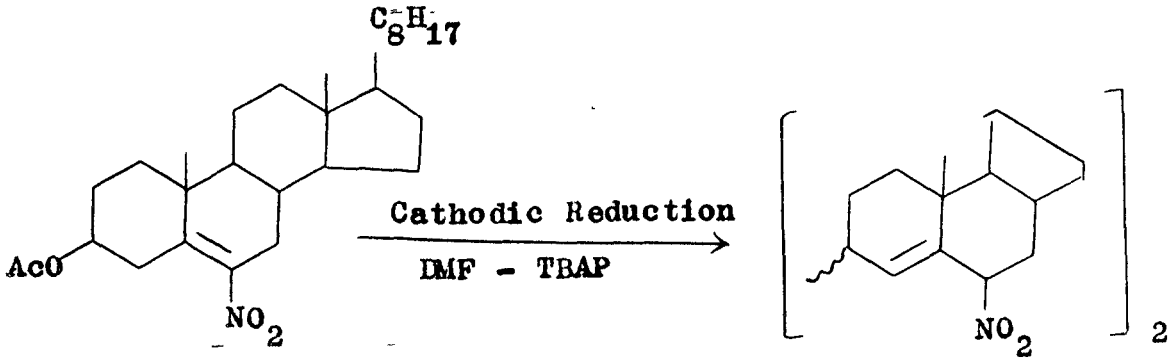
	R	Y
(LXXVI)	OAc	Cl
(LXXVII)	Cl	Cl
(LXXVIII)	H	Cl
(LXXIX)	OAc	Br

Pinhey et al.[25] reported that the treatment of 6β-nitrocholest-4-ene (LXXX) with catalytic amount of sodium methoxide in methanol gave an equilibrium mixture which contained the starting material (LXXX) and the 6α-epimer (LXXXI) in 1:1 ratio. According to them 6α-nitrosteroid is thermodynamically more stable than its 6β-epimer.

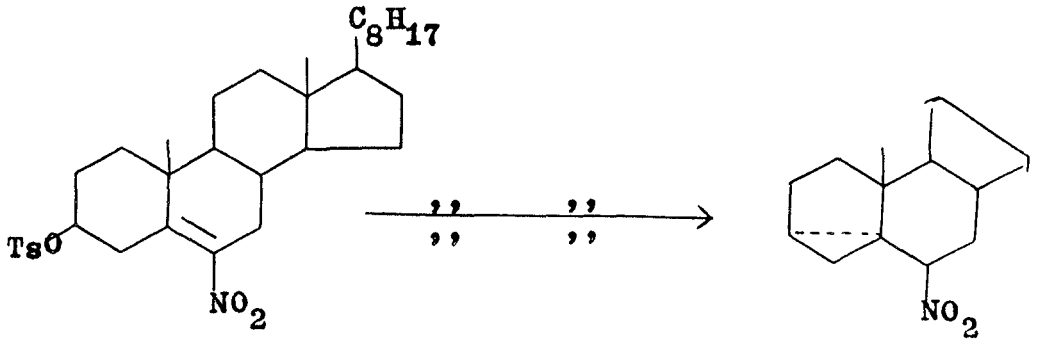


(LXXX) (LXXXI)

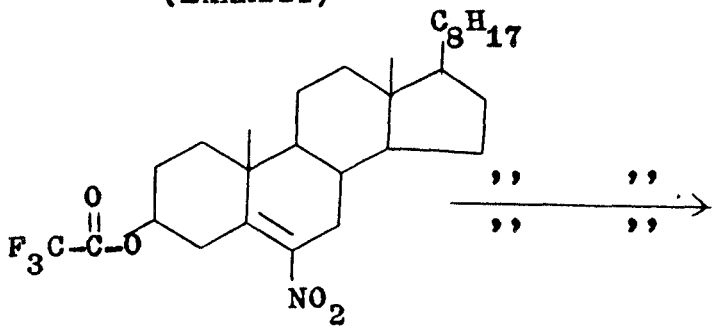
Recently Takeo and coworkers[26] carried out the reduction of homoallylic nitroesters in DMF-TBAP using platinum electrodes whereas 3β-acetoxy 6-nitrocholest-5-ene (XLVI) gave a 3,3'-dimer (LXXXII), 3β-tosylate (LXXXIII) gave 6β-nitro-3α,5-cyclo-5α-cholestane (LXXXIV), 3β-trifluoroacetate (LXXXV) showed intermediate behaviour and gave both (LXXXII) and (LXXXIV). Similarly (LXXXVI) gave 5β,19-cyclosteroid (LXXXVII).



(XLVI) (LXXXII)

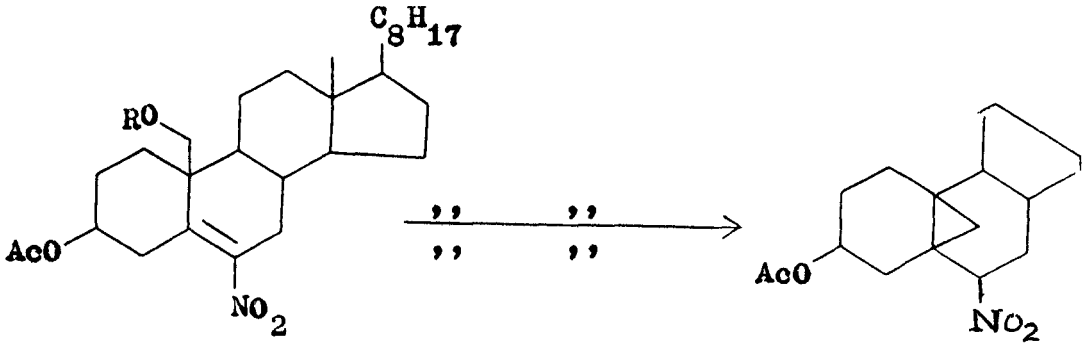


(LXXXIII) (LXXXIV)



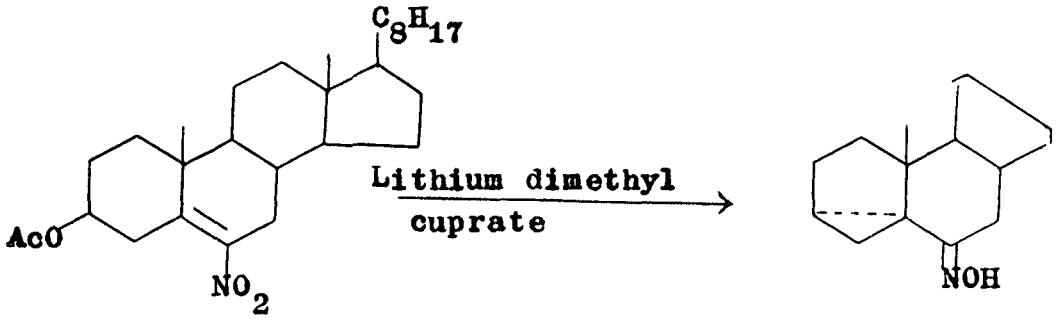
(LXXXII) + (LXXXIV)

(LXXXV)

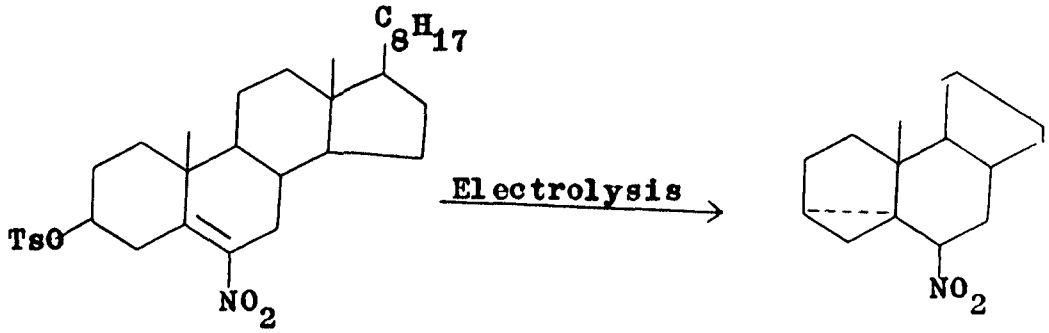


(LXXXVI) (LXXXVII)

Stiver and Yates[27] reported that treatment of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with an excess of lithium dimethyl cuprate gave 3α,5-cyclo-5α-cholestan-6-one oxime (LVIIIb) and electrolysis of the toluene-p-sulphonate (LXXXIII) gave (LXXXIV).



(XLVI) (LVIIIb)

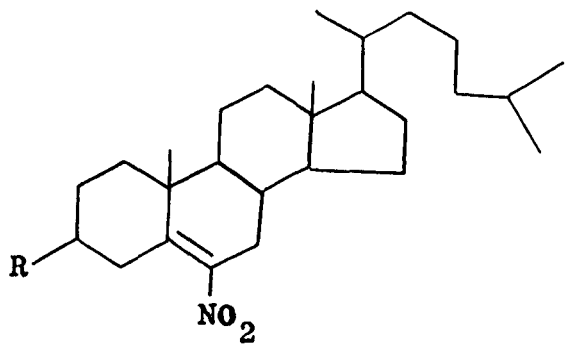


(LXXXIII) (LXXXIV)

Discussion

(A) Allylic bromination and Dehydrobromination of 6-nitroolefins

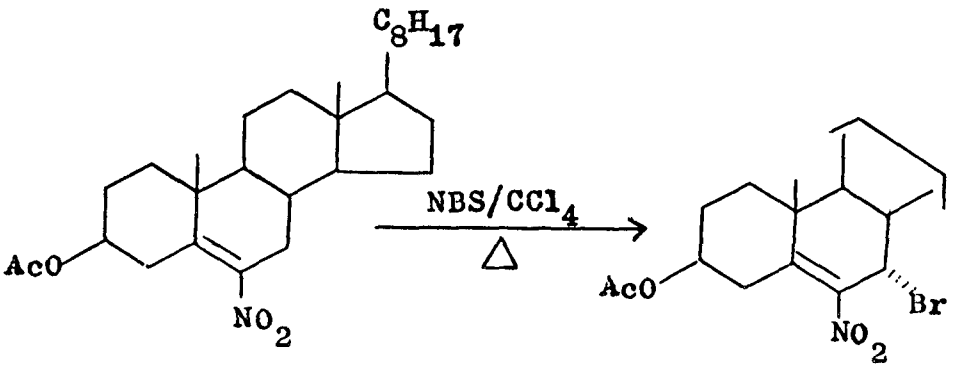
Halogenation of ketones at α-position and subsequent dehydrohalogenation by base is frequently employed to create unsaturated centres adjacent to ketonic functions. Such operations have been of immense utility in the field of steroids.[28] Bromination of ketones[29-55] provided a number of normal as well as abnormal products. No attempts have been made for such type of study with unsaturated nitro compounds. We considered it expedient to prepare some nitrosteroids with bromines at α - and β -positions and subject them to dehydrohalogenation. In this connection, allylic bromination of 3β-acetoxy-6-nitrocholest-5-ene (XLVI), 3β-chloro-6-nitrocholest-5-ene (LXXIV) and 6-nitrocholest-5-ene (LXXV) was carried out in the present study.



	R
(XLVI)	OAc
(LXXIV)	Cl
(LXXV)	H

Bromination of 3β-acetoxy-6-nitrocholest-5-ene (XLVI)

A mixture of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) N-bromosuccinimide, and benzoyl peroxide (as catalyst) in carbon tetrachloride was refluxed for 3 hours. The solid material was filtered and filterate was evaporated to obtain a residue which was chromatographed over silica gel to provide fine crystalline compound, m.p. 165°.



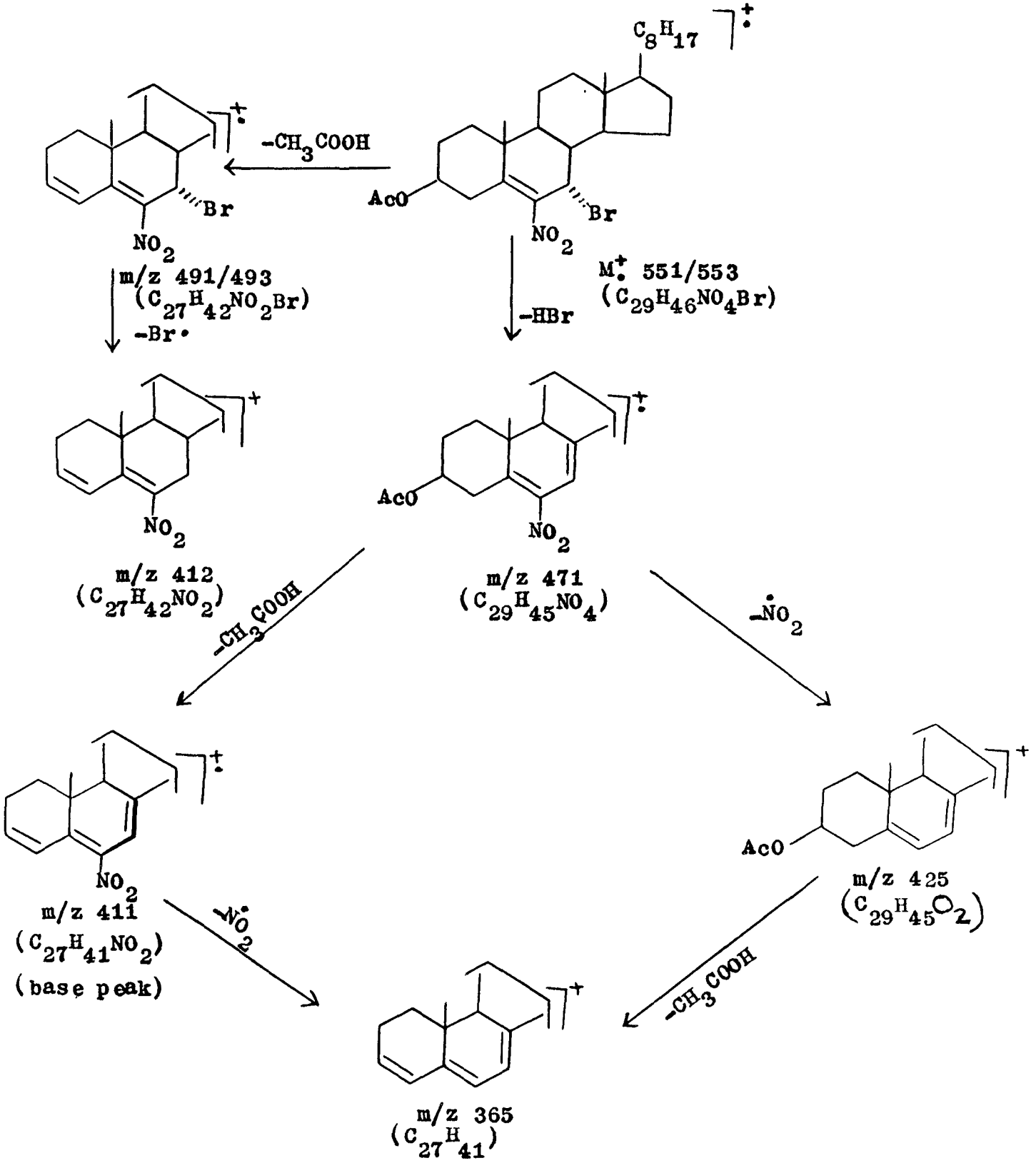
(XLVI) (LXXXVIII)

Characterization of the compound, m.p. 165° as 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII)

The compound, m.p. 165° (positive Beilstein test) was analysed correctly for $C_{29}H_{46}NO_4Br$. The molecular ion peaks M^+ (551/553) supports its molecular composition. From

the composition it was evident that one bromine was introduced into parent compound (XLVI). The I.R. spectrum of the compound exhibited absorption bands at 1740 ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1655 (C=C), 1240 (C-O), and 675 cm^{-1} (C-Br). Two strong bands at 1515 and 1375 cm^{-1} correspond to the symmetric and asymmetric stretching of ($C-NO_2$) group.[56] The N.M.R. spectrum displayed a broad singlet at δ 5.08 (C7-βH; $W_{\frac{1}{2}}$ = 3 Hz; equatorial) which suggests the presence of bromine at C7 position as axial. The dreiding model of (LXXXVIII) showed dihedral angle between C7-βH and C8-βH to be almost 90° which accounts for non split of C7-β-proton.[57] An additional evidence for the presence of axial bromine was given by the I.R. spectrum which showed C-Br absorption frequency at 675 cm^{-1}. It is known that axial bromine leads to bands in the 590-690 cm^{-1} whereas equatorial substitution results the absorption in 750-700 cm^{-1} range.[58] Further the bromine at C7 has been assumed to be (α) oriented in the view of its C.D. curve which showed a negative cotton effect (λ254 nm).[59] A multiplet centred at δ 4.67 ($W_{\frac{1}{2}}$ = 18 Hz) integrating for one proton was assigned to C3-αH. A sharp singlet for ($CH_3-\underset{\underset{O}{\|}}{C}-O$) appeared at δ 2.0. The methyl protons were observed at δ 1.18 (C10-CH_3), 0.73 (C13-CH_3), 0.83 and 0.91 (remaining methyl protons). On the basis of the foregoing discussion, this compound was regarded to be 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII).

Scheme-1


C8H17
-CH3COOH
AcO
Br
NO2
m/z 491/493
(C27H42NO2Br)
-Br•
M+• 551/553
(C29H46NO4Br)
-HBr
m/z 412
(C27H42NO2)
m/z 471
(C29H45NO4)
-CH3COOH
-NO2
m/z 411
(C27H41NO2)
(base peak)
-NO2
m/z 425
(C29H45O2)
-CH3COOH
m/z 365
(C27H41)

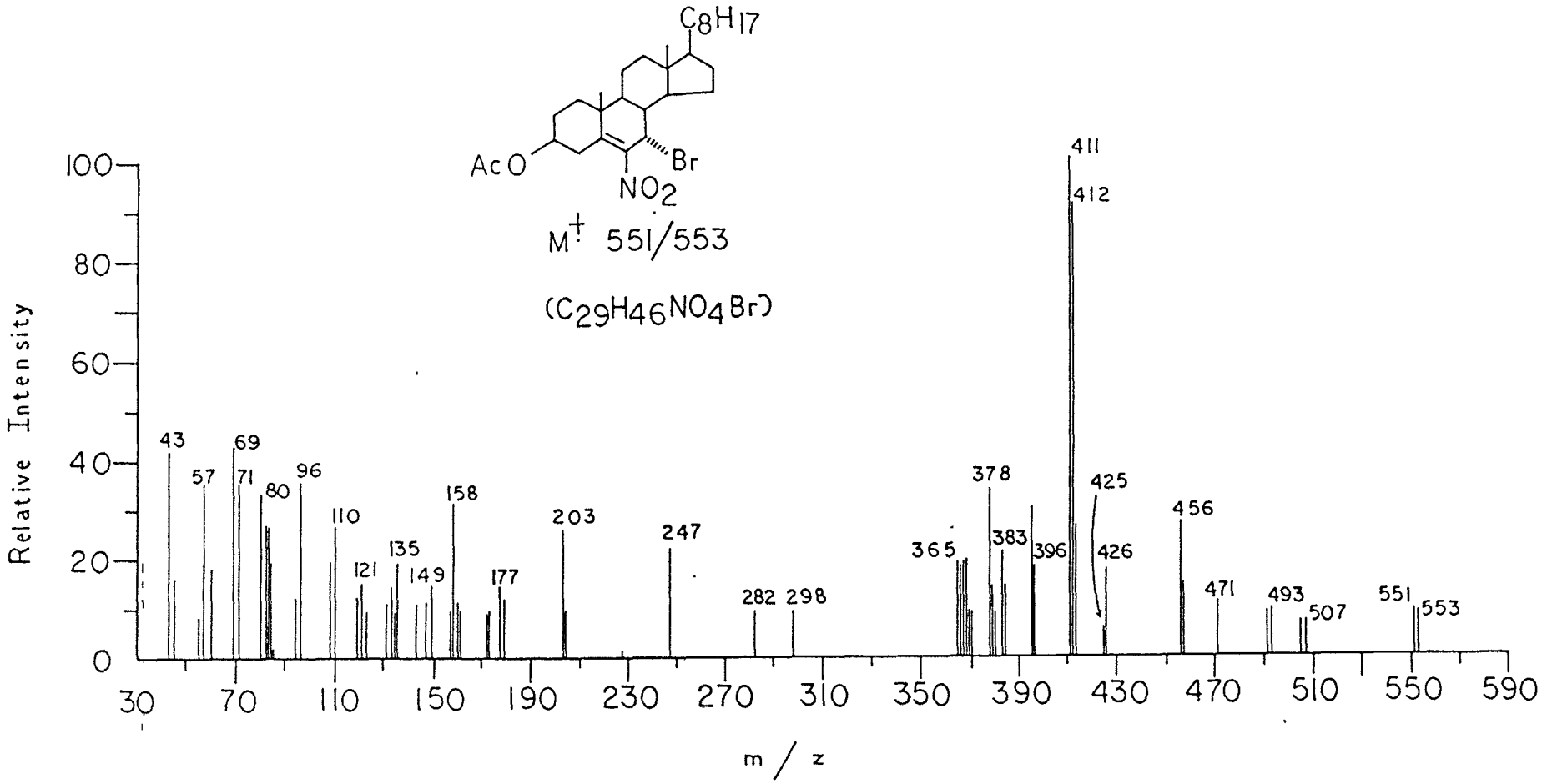
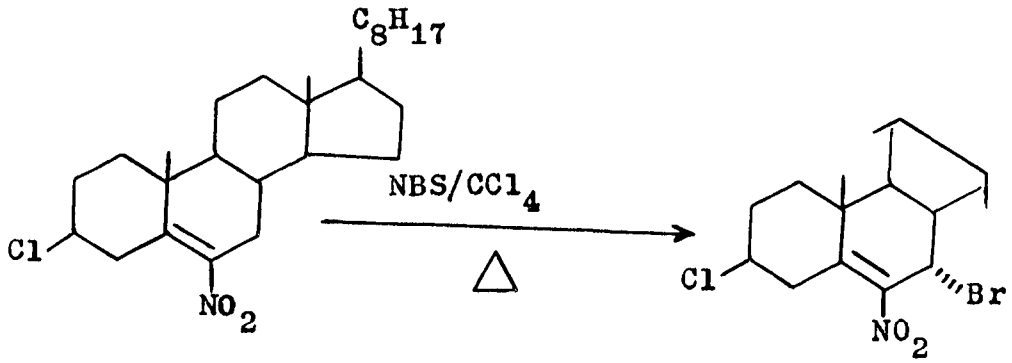


Fig. 1 Mass Spectrum of LXXXVIII.

Further evidence in support of structure (LXXXVIII) was found by its mass spectrum. The mass spectrum of compound (LXXXVIII) (Fig. 1) showed molecular ion peaks at 551/553 (1:1)($C_{29}H_{46}NO_4Br$) along with significant peaks at m/z 491/493 (1:1) (M^+ -CH_3COOH), m/z 411 (m/z 491/493-HBr; base peak), m/z 412 (m/z 491/493-Br), m/z 396 (m/z 411-CH_3), m/z 365 (m/z 411-NO_2), m/z 471 (M^+-HBr), m/z 425 (m/z 471-NO_2), m/z 365 (m/z 425-CH_3COOH), m/z 411 (m/z 471-CH_3-COOH), m/z 456 (m/z 471-CH_3) and other lower mass peaks. Formation of some of the fragment ions has been shown in Scheme - 1 which is tentative in nature.

Bromination of 3β-chloro-6-nitrocholest-5-ene (LXXV)

The bromination of 3β-chloro-6-nitrocholest-5-ene (LXXIV) was carried out in a manner described for the nitro olefin (XLVIII). It provided fine crystals of a compound, m.p. 167°.



(LXXIV) (LXXXIX)

Characterization of the compound, m.p. 167° as 3β-chloro-7α-bromo-6-nitrocholest-5-ene (LXXXIX)

The compound, m.p. 167° showed elemental analysis, compatible with formula $C_{27}H_{43}NO_2BrCl$ (positive Beilstein test) which suggested the insertion of one bromine atom into the substrate (LXXIV). In I.R. spectrum, the C-Br frequency was observed at 665 cm^{-1} which proved the presence of bromine as axial.[58] Other bands at 1660, 760, 1515 and 1375 cm^{-1} were ascribable to C=C, C-Cl, and C-NO_2 stretching frequencies respectively. In N.M.R. spectrum a broad singlet was observed at δ 5.12 ascribable to C7-β$\underline{H}$. Stereochemistry of bromine was determined on the basis of C.D. curve which showed negative cotton effect and thus bromine at C7 was taken as to be (α) oriented. A multiplet centred at δ 4.0 ($W\frac{1}{2}$ = 17 Hz) integrating for one proton was assigned to C3α-$\underline{H}$. The angular methyl protons were observed at δ 1.2 (C10-C$\underline{H}_3$), 0.73 (C13-C$\underline{H}_3$), 0.83 and 0.93 (remaining methyl protons).

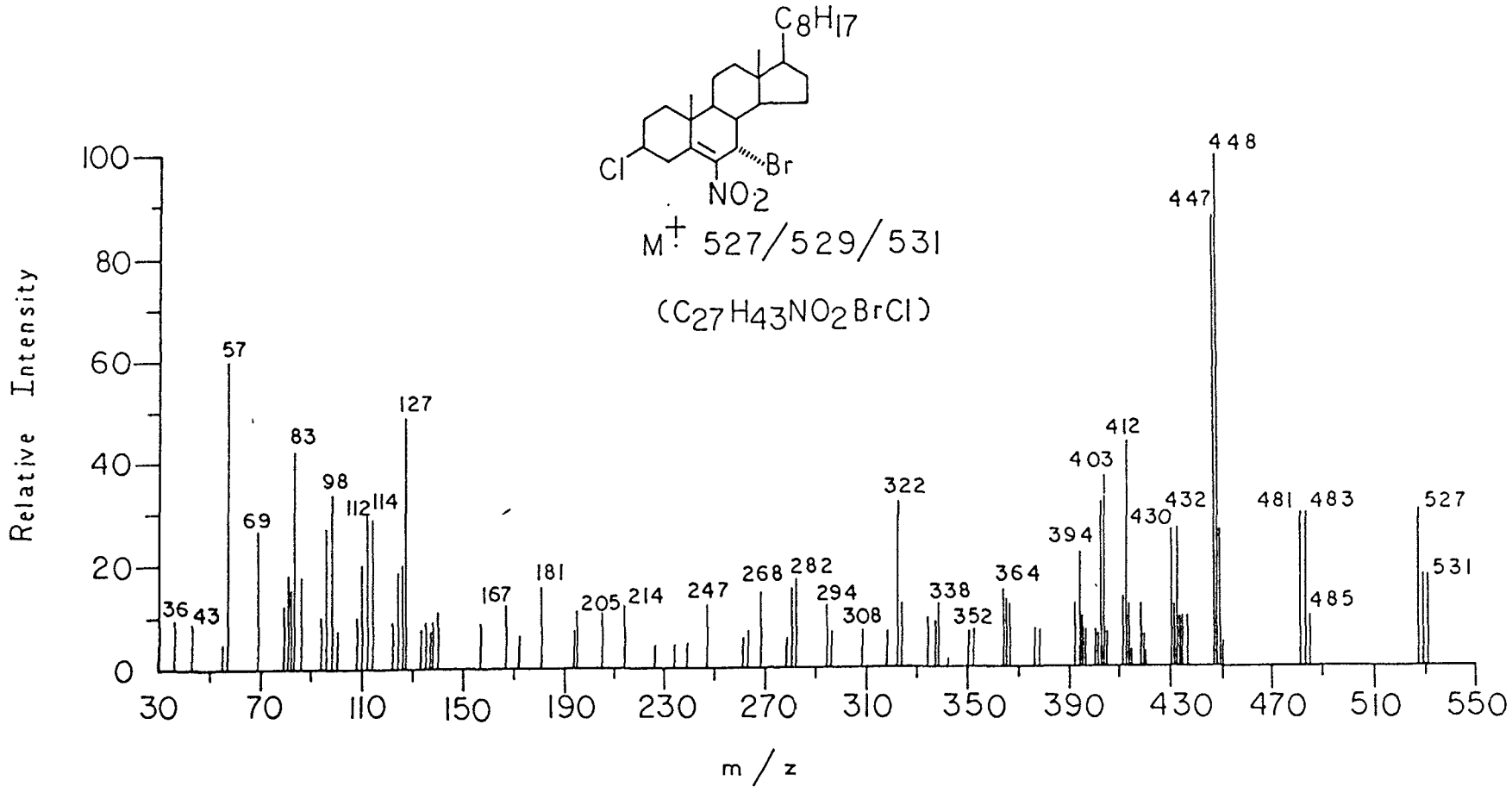


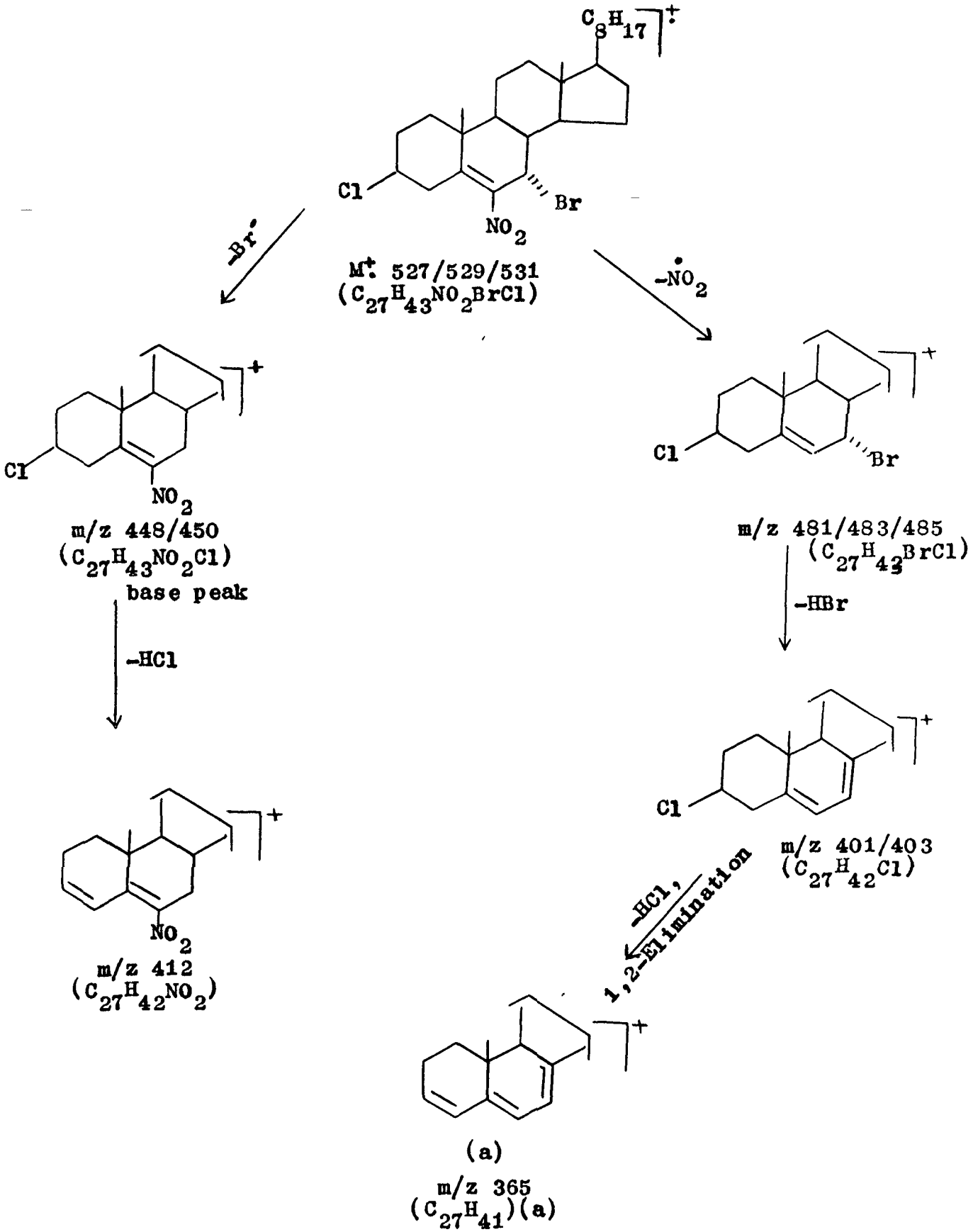
Fig.2 Mass Spectrum of LXXXIX.

Further evidence in support of structure (LXXXIX) was found by mass spectrum. The compound (LXXXIX) (Fig. 2) showed molecular ion peaks at m/z 527/529/531 along with significant peaks at m/z 481/483/485 (M^{+} $-NO_2$), m/z 401/403 (m/z 481/483/485-HBr), m/z 365 (m/z 401/403-HCl), m/z 350 (m/z 365-CH_3), m/z 448 (base peak)/450 (M^{+} -Br), m/z 412 (m/z 448/450-HCl) and lower mass peaks.

m/z 481/483/485, 401/403, 365 and 350

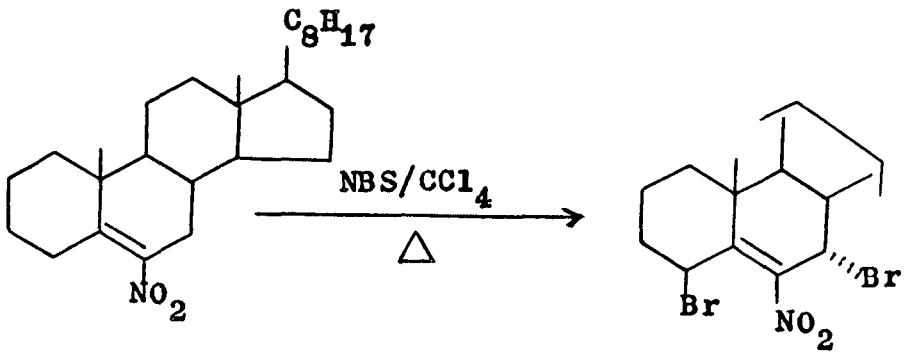
The formation of the fragment ions m/z 481/483/485 can be suggested by the loss of nitro group from the molecular ion and the fragment ion peaks 401/403 represent the loss of HBr from the ion m/z 481/483/485. The fragment ion peak at 365 formed by the loss of HCl from the ion m/z 401/403. Loss of HCl from chlorides usually involved 1,4 and 1,3 elimination.[60] However, in this case it is reasonable to assume that the loss occurs by 1,2-elimination thus giving rise to a more conjugated species (a) Scheme-2.

Scheme - 2


C8H17
Cl
Br
NO2
-Br·
M+· 527/529/531
(C27H43NO2BrCl)
-·NO2
Cl
NO2
m/z 448/450
(C27H43NO2Cl)
base peak
-HCl
Cl
Br
m/z 481/483/485
(C27H43BrCl)
-HBr
Cl
m/z 401/403
(C27H42Cl)
-HCl,
1,2-Elimination
NO2
m/z 412
(C27H42NO2)
(a)
m/z 365
(C27H41)(a)

Bromination of 6-nitrocholest-5-ene (LXXV)

6-Nitrocholest-5-ene (LXXV) was refluxed with NBS in usual manner. Reaction mixture after usual work up and column chromatography afforded a compound, m.p. 143°.



(LXXV) (XC)

Characterization of the compound, m.p. 143° as 4β,7α-dibromo-6-nitrocholest-5-ene (XC)

The compound, m.p. 143° was analysed for $C_{27}H_{43}NO_2Br_2$ (positive Beilstein test). From the molecular composition, addition of two bromine atoms was indicated. The C-Br, C=C, and C-NO_2 stretching bands were seen at 612, 1625, 1525 and 1375 cm^{-1} respectively. The N.M.R. spectrum of the compound

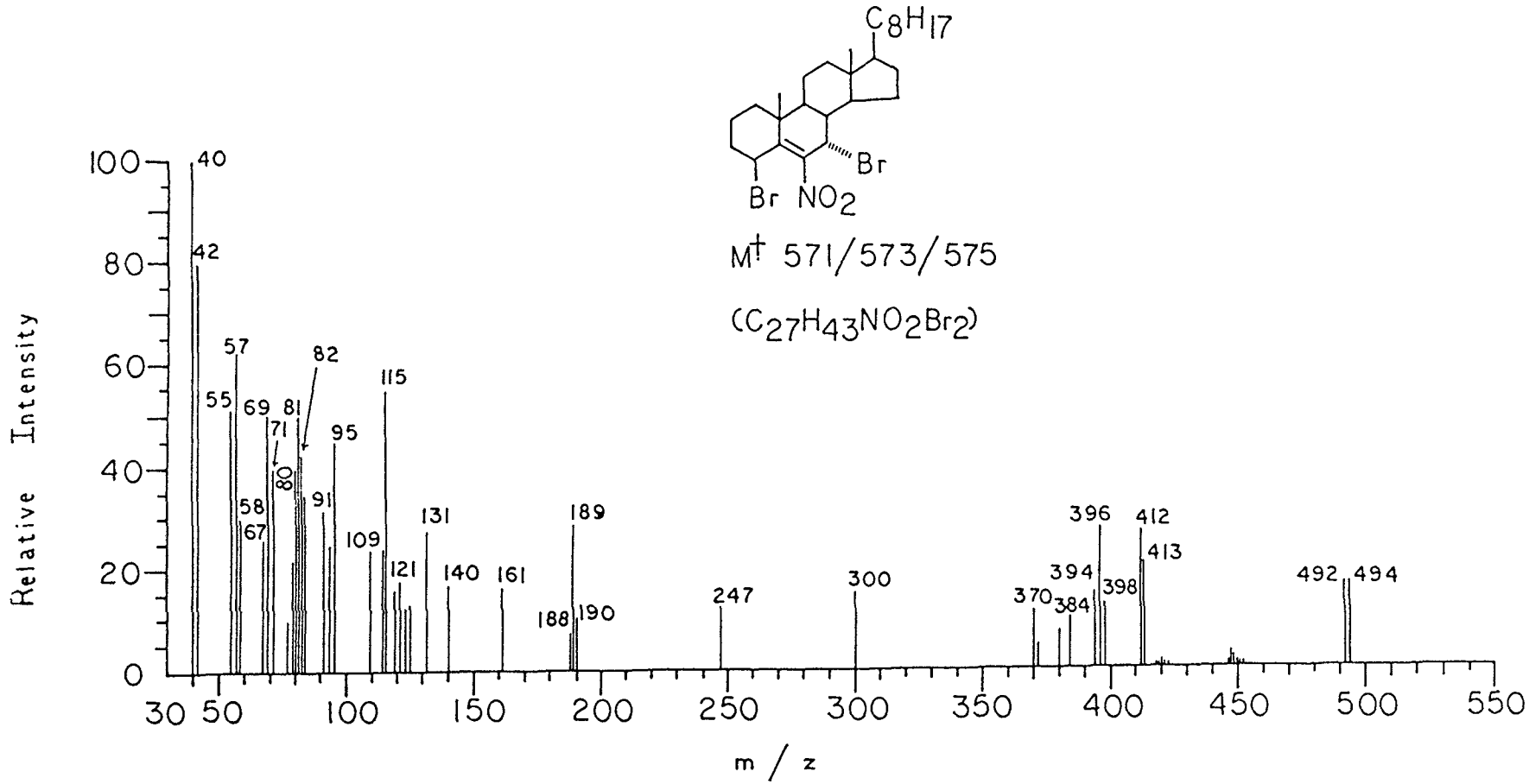


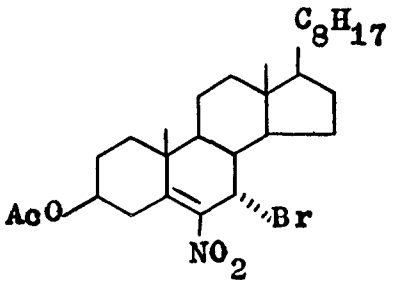
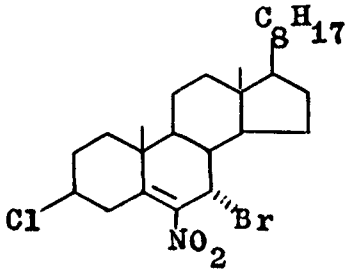
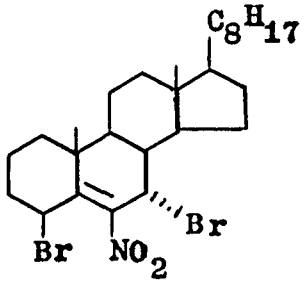
Fig. 3 Mass Spectrum of (XC).

(XC) displayed two broad singlets integrating for one proton at δ 5.05 and 5.56. The former signal was in the close agreement with δ value observed for C7 proton in compounds (LXXXVIII-IX) which clearly indicated the attachment of bromine at C7 with axial (α) orientation ($W\frac{1}{2}$ = 3 Hz). The latter signal at δ 5.56 can be assigned to C4-proton. The half band width of the signal was found to be 4 Hz. This suggested the equatorial nature of C4 proton giving β-orientation (axial) to C4 bromine.[57] Angular methyl signals appeared at δ 1.55 (C10-$\underline{CH}_3$), 0.71 (C13-$\underline{CH}_3$), 0.83 and 0.91 (remaining methyl protons). The mass spectrum of 4β,7α-dibromo-6-nitrocholest-5-ene (XC) (Fig. 3) did not give the molecular ion peaks at m/z 571/573/575 ($C_{27}H_{43}NO_2Br_2$). Significant peaks were observed at m/z 492/494 (1:1) (M-$\dot{B}r$), m/z 412 (m/z 492/494-HBr), m/z 413 (m/z 492/494-Br) and lower mass peaks.

Mention here may be made of important feature of the N.M.R. spectra of the compounds (LXXVIII, LXXXIX, XC). The C10-methyl resonance moves to downfield due to the functionality in Ring A and B.[57] Resonance due to C10-methyl and C4 and C7 protons in N.M.R. spectra of the compounds (LXXVIII, LXXXIX, XC) is given in Table 1.

Table - 1

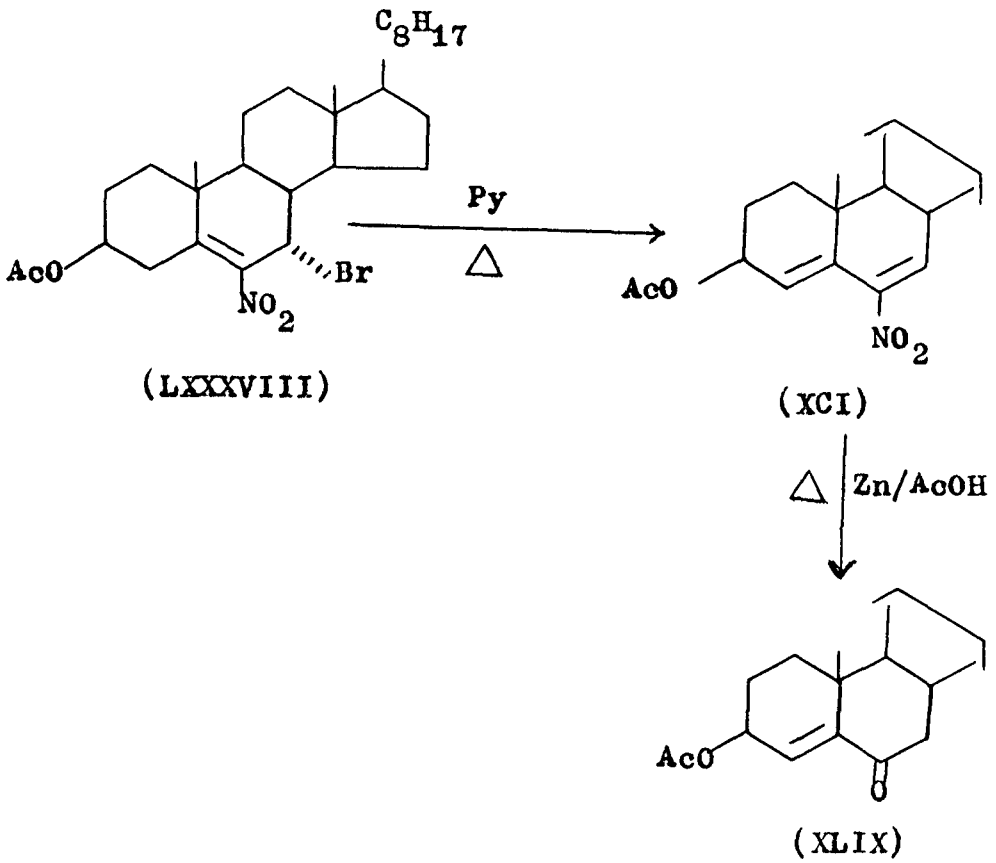
Chemical shifts of C10-methyl and C4 and C7 protons in (LXXXVIII, LXXXIX, XC) at 60 MHz

Compound	Chemical shift (ppm)		
	C10-methyl	C4 proton	C7 proton
 (LXXXVIII)	1.18	-	5.08
 (LXXXIX)	1.20	-	5.12
 (XC)	1.55	5.56	5.05

It can be seen from the above data (Table - 1) that C10-methyl signal in compound (XC) appeared at lower field than that for the compounds (LXXXVIII) and (LXXXIX). This downfield shift of methyl resonance in compound (XC) may be due to C4β-bromine (axial) which causes large deshielding at C10-methyl protons.[61]

Treatment of 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII) with pyridine

The compound (LXXXVIII), m.p. 165° was refluxed with pyridine for 2 hours and after usual work up of the reaction mixture and subsequent column chromatography, a single compound, m.p. 103°, was obtained.



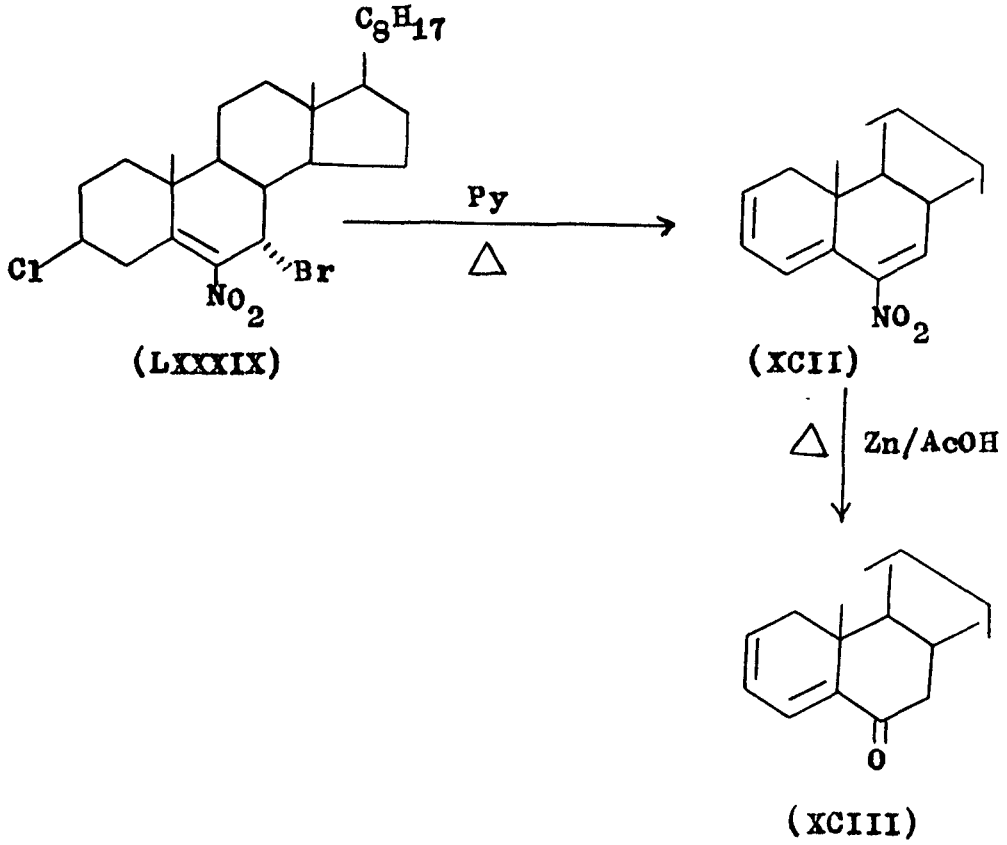
(LXXXVIII) (XCI) (XLIX)

Characterization of the compound, m.p. 103° as 3β-acetoxy-6-nitrocholesta-4,6-diene (XCI)

The compound, m.p. 103° was analysed for $C_{29}H_{45}NO_4$. Negative Beilstein test showed that the bromine was lost. In its I.R. spectrum absorption bands appeared at 1730 ($CH_3-\overset{O}{\overset{\|}{C}}-O$), 1225 (C-O), 1615 (C=C), 1510 and 1370 cm^{-1} ($C-NO_2$). The N.M.R. spectrum exhibited a multiplet centred at δ 5.33 integrating for one proton and was assigned to C3-αH ($W\frac{1}{2}$ = 16 Hz). Two unresolved singlets were observed at δ 6.43 and 5.72 ascribable to C7-H and C4-H respectively. A sharp singlet at δ 2.03 for three protons was assigned to $CH_3-\overset{O}{\overset{\|}{C}}-O$. The methyl signals were seen at δ 1.05 ($C10-CH_3$), 0.75 ($C13-CH_3$), 0.83 and 0.91 (remaining methyl protons). From the above data it was evident that the compound, m.p. 103° may be 3β-acetoxy-6-nitrocholesta-4,6-diene (XCI). Further this proposal was chemically supported by transformation of (XCI) into the known ketone (XLIX)[62] on ketonization with Zn/AcOH.

Treatment of 3β-chloro-7α-bromo-6-nitrocholest-5-ene (LXXXIX) with pyridine

3β-Chloro-7α-bromo-6-nitrocholest-5-ene (LXXXIX), m.p. 167° was refluxed with pyridine. The reaction mixture after usual work up and column chromatography gave an oil.



(LXXXIX) (XCII) (XCIII)

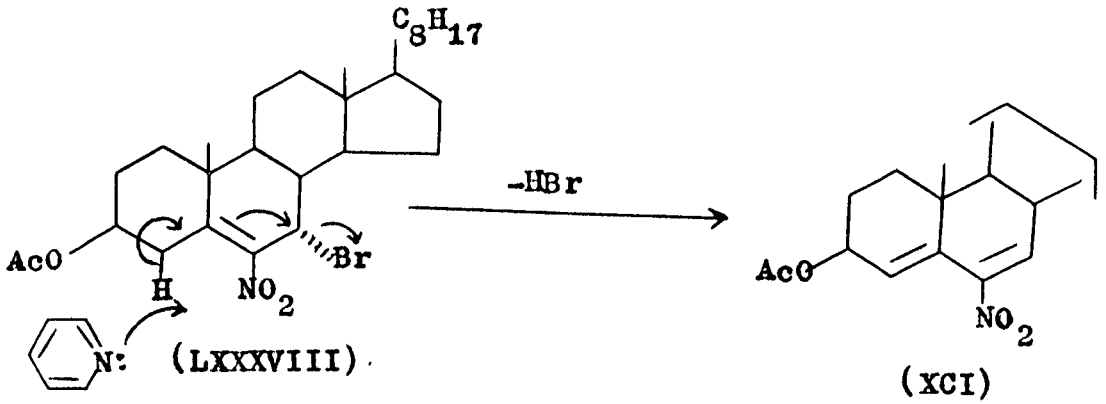
Characterization of the oil as 6-nitrocholesta-2,4,6-triene (XCII)

The compound (XCII) was analysed for $C_{27}H_{41}NO_2$. Negative Beilstein test showed that the bromine and chlorine atoms were lost during the reaction. Its I.R. spectrum showed bands at 1642 (C=C-C=C-C(NO$_2$) = C), 1540 and 1390 cm^{-1} (C-NO_2). The N.M.R. spectrum displayed a singlet for C7-vinylic proton at δ 5.7. The C2, C3 and C4 vinylic protons were observed between δ 6.2 to 7.0 as multiplets. Methyl signals were observed at δ 1.05 (C10-CH_3), 0.66 (C13-CH_3), 0.83 and 0.93 (remaining

methyl protons). Compound (XCII) was treated with Zn/AcOH under reflux and afforded the known ketone (XCIII).[63] On the basis of molecular composition, spectral and chemical evidences, the compound (XCII) was characterized as 6-nitrocholesta-2,4,6-triene which was obtained by the loss of HBr and HCl from (LXXXIX).

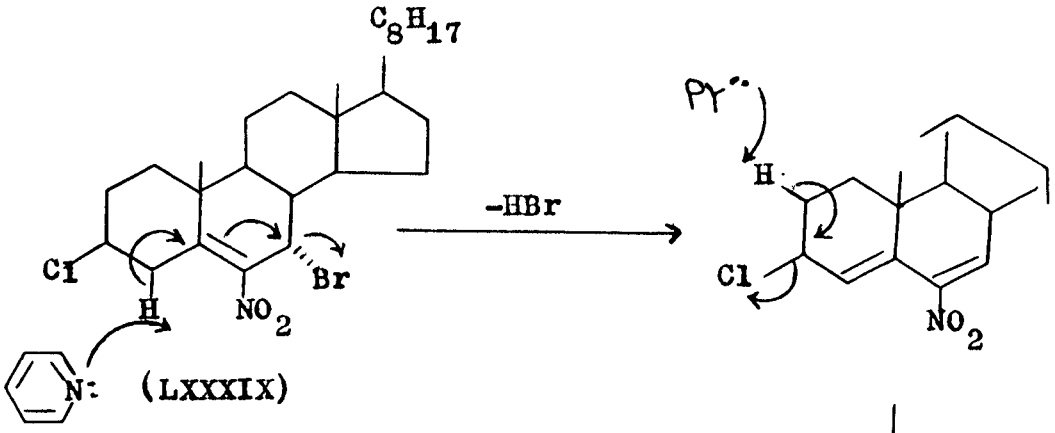
The compounds (LXXXVIII) and (LXXXIX) gave diene and triene respectively on treatment with pyridine. A tentative mechanism is being proposed (Scheme - 3) to account for the formation of 3β-acetoxy-6-nitrocholesta-4,6-diene (XCI) and 6-nitrocholesta-2,4,6-triene (XCII) from 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII) and 3β-chloro-7α-bromo-6-nitrocholest-5-ene (LXXXIX).

Scheme - 3



(LXXXVIII)

(XCI)



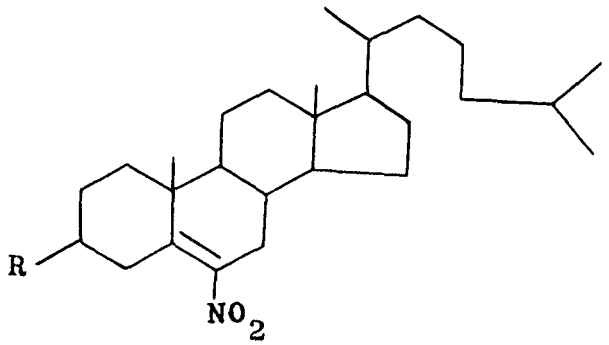
(LXXXIX)

-HCl

(XCII)

(B) Oxidation of 6-nitroolefins with lead (IV) acetate

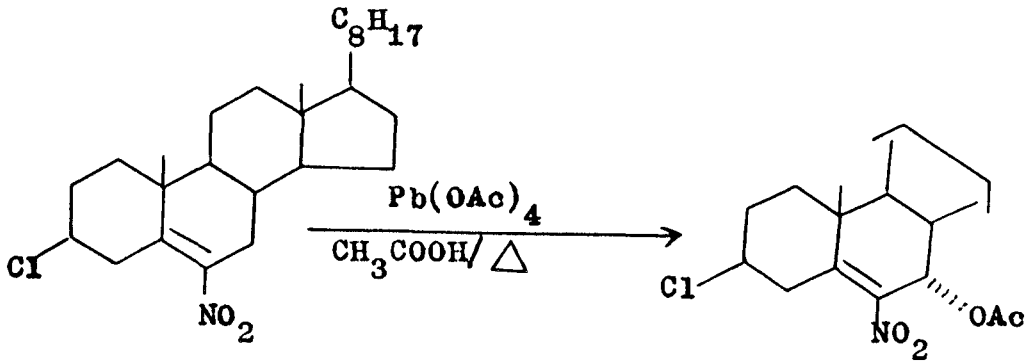
In the recent past, great interest has been shown to the reaction of lead (IV) acetate with olefins[64], ketones,[65] oximes,[67-69] alcoholes[70-78] and lactones.[79] No significant work has been done, however, with steroidal nitro olefins. This prompted us to study the reaction of lead (IV) acetate with 3β-chloro-6-nitrocholest-5-ene (LXXIV), 3β-acetoxy-6-nitrocholest-5-ene (LXVI) and 6-nitrocholest-5-ene (LXXV).



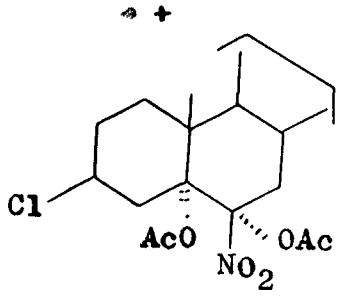
	R
(LXXIV)	Cl
(XLVI)	OAc
(LXXV)	H

Reaction of 3β-chloro-6-nitrocholest-5-ene (LXXIV) with $Pb(OAc)_4$-potassium acetate

The reaction of 3β-chloro-6-nitrocholest-5-ene (LXXIV) with lead (IV) acetate and subsequent column chromatography over silica gel provided three non crystallizable oils (XCIV, XCV and XCVI).

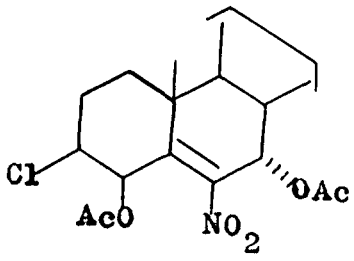


(LXXIV) (XCIV)



(XCV)

+



(XCVI)

Characterization of the compound (XCIV) as 3β-chloro-7α-acetoxy-6-nitrocholest-5-ene

The compound (XCIV) was analysed for $C_{29}H_{46}NO_4Cl$ (positive Beilstein test). The molecular composition indicated the addition of one acetoxy group to the substrate (LXXIV). The strong bands at 1745, 1270-1210 cm^{-1} [80] in the I.R. spectrum further signified the presence of acetoxy group in the compound (XCIV). Other bands at 710, 1510 and 1365 cm^{-1} were ascribable to C-Cl and $C-NO_2$ stretching respectively. The N.M.R. spectrum displayed a singlet at δ 2.1 ($C\underline{H}_3-\overset{O}{\overset{\|}{C}}-O$), and a broad singlet at δ5.65 integrating for one proton, was assigned to C7-proton. The drieding model of (XCIV) showed the dihedral angle between C7-β$\underline{H}$ and C8-β$\underline{H}$ to be almost 90° which accounts for the non split signal of the C7-β-proton. Therefore, the acetoxy group at C7 is axial (α) oriented. The angular methyl protons were seen at δ 1.15 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.81 and 0.91 (remaining methyl protons). On the basis of the foregoing discussion, this compound (XCIV) was regarded to be 3β-chloro-7α-acetoxy-6-nitrocholest-5-ene.

Characterization of the compound (XCV) as 3β-chloro-5,6α-diacetoxy-6-nitrocholestane

The compound (XCV) was analysed for $C_{31}H_{48}NO_6Cl$. From the analysis, it was evident that the addition of two acetoxy groups to the parent compound (LXXIV) has occurred. The I.R. spectrum had strong bands at 1730, 1280-1220 ($CH_3-\overset{O}{\overset{\|}{C}}-O$), 715 (C-Cl), 1510 and 1365 cm^{-1} ($C-NO_2$). The N.M.R. spectrum showed a strong singlet at δ 1.96 with two notches at δ 2.0 and at δ 1.93 integrating for six protons of the two acetoxy groups at C5 and C6. The configuration of the C5 acetoxy group has been considered as axial on the basis of the C3-proton, which appeared at δ 4.10 as multiplet having a half band width of 18 Hz. Evidently, the C3 proton is axial (α) oriented and A/B ring junction is trans,[57] rendering the acetoxy group -α-oriented. The angular methyl protons were observed at δ 1.16 (C10-CH_3), 0.68 (C13-CH_3), 0.81 and 0.93 (remaining methyl protons).

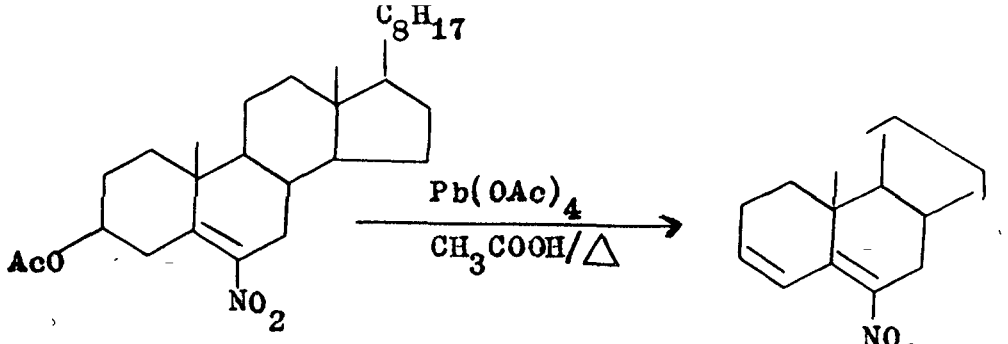
Characterization of the compound (XCVI) as 3β-chloro-4β,7α-diacetoxy-6-nitrocholest-5-ene

The compound (XCVI) was analysed for $C_{31}H_{48}NO_6Cl$ (positive Beilstein test). From the composition, addition of two acetoxy groups to the parent compound (LXXIV) was

indicated. The I.R. spectrum had strong bands at 1730, 1230 ($CH_3-\overset{O}{\overset{\|}{C}}-O$), 740 (C-Cl), 1645 (C=C) and 1510, 1370 cm^{-1} ($C-NO_2$). The N.M.R. spectrum displayed a broad singlet integrating for one proton at δ 4.50 for C7-βH ($W\frac{1}{2}$ = 3 Hz, equatorial) suggesting axial configuration for C7-acetoxy. A multiplet appeared at δ 4.50 for C3-αH ($W\frac{1}{2}$ = 8 Hz; axial). A doublet which appeared at δ 5.76 integrating for one proton, was assigned to C4-αH (J = 3 Hz, equatorial) and a singlet at δ 2.03 with two notches at δ 1.96 and at δ 2.10, integrating for six protons, corresponds to two acetoxy group at C-4 and C-7. The angular methyl protons were observed at δ 1.26 (C10-CH_3), 0.70 (C13-CH_3), 0.95 and 0.85 (remaining methyls). On the basis of elemental analysis and spectral evidences, the compound (XCVI) was characterized as 3β-chloro-4β-7α-diacetoxy-6-nitrocholest-5-ene.

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with $Pb(OAc)_4$-potassium acetate

3β-Acetoxycholest-5-ene (XLVI) was treated with lead tetraacetate in acetic acid in the presence of potassium acetate under reflux for 12 hrs. After the usual work up and column chromatography over silica gel, the reaction mixture provided single compound m.p. 72°.



(XLVI) (L)

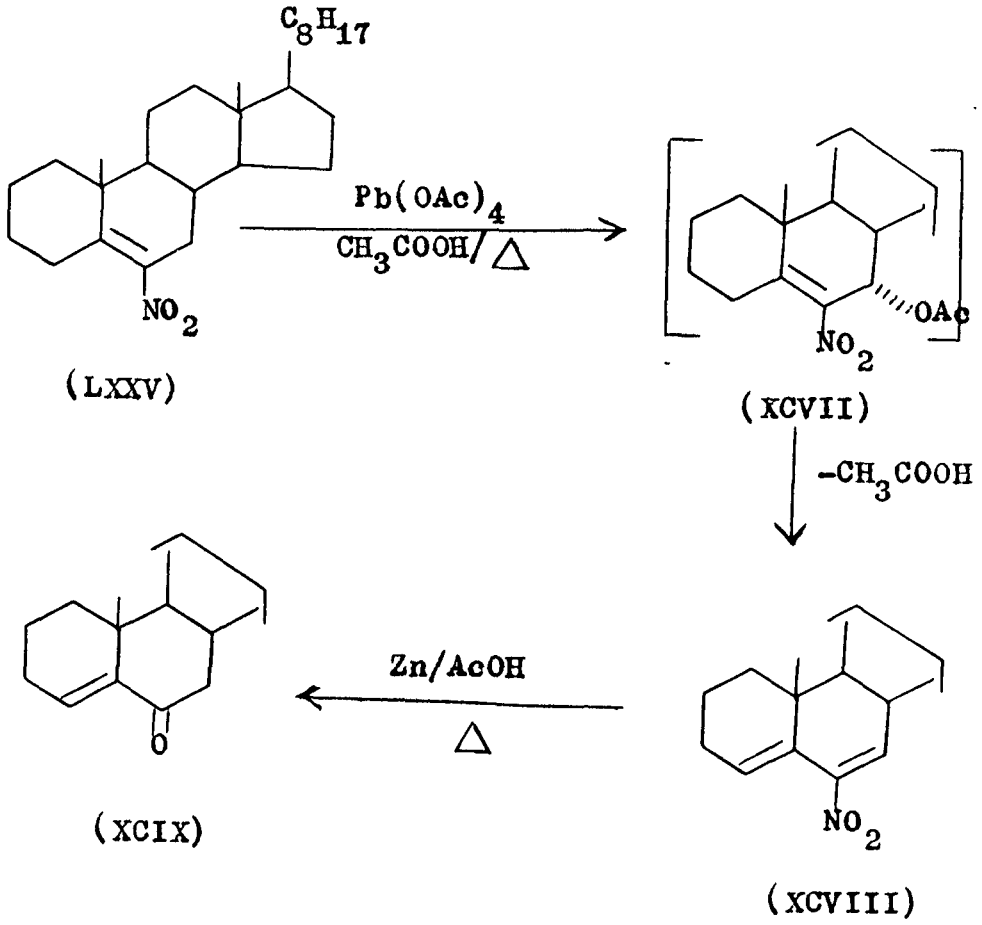
Characterization of the compound, m.p. 72° as 6-nitrocholesta-3,5-diene (L)

The compound, m.p. 72° was analysed for $C_{27}H_{43}NO_2$. Its I.R. spectrum showed absorption bands at 1680 (C=C-C=C-), 1508 and 1360 cm^{-1} (C-NO_2). The absence of acetate stretching bands in its I.R. spectrum indicated that the acetate group was lost from parent compound (XLVI). In N.M.R. spectrum the C-4 vinylic proton was observed at δ 6.5 as a doublet (J=10 Hz). The C-3 proton appeared as a multiplet at δ 6.1. Methyl signals were observed at δ 1.08 (C10-CH_3), 0.7 (C13-CH_3), 0.95 and 0.83 (remaining methyls). From the above data it was evident that the compound, m.p. 72°

was 6-nitrocholesta-3,5-diene (L) which was further confirmed by comparison with its authentic sample[15].

Reaction of 6-nitrocholest-5-ene (LXXV) with $Pb(OAc)_4$-potassium acetate

Reaction of 6-nitrocholest-5-ene (LXXV) with $Pb(OAc)_4$ was performed in the presence of potassium acetate for 12 hrs under reflux. After usual work up and column chromatography over silica gel, in addition to some unreacted compound (LXXV), a compound, m.p. 76° was obtained.



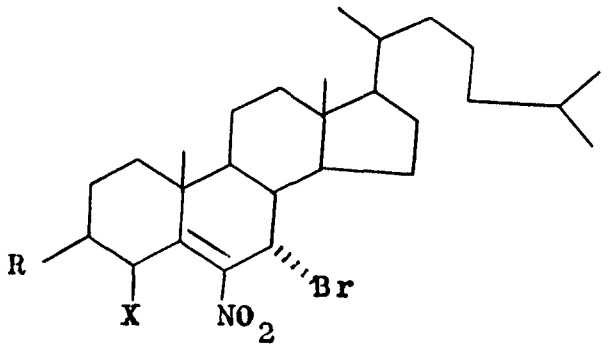
(LXXV) (XCVII) (XCVIII) (XCIX)

Characterization of the compound, m.p. 76° as 6-nitrocholesta,4,6-diene (XCVIII)

The compound, m.p. 76° was analysed for $C_{27}H_{43}NO_2$. The I.R. spectrum showed bands at 1680 (C=C-C=C-), 1515 and 1365 cm^{-1} ($C-NO_2$). The N.M.R. spectrum exhibited a broad singlet at δ 5.30 which was assigned to C7 proton. The C4 proton appeared as multiplet at δ 5.75. Angular methyl protons were seen at δ 1.21 (C10-CH_3), 0.73 (C13-CH_3), 1.0 and 0.8 (remaining methyls). Compound (XCVIII) when treated with Zn-AcOH afforded a known ketone (XCIX).[63] From these observations the compound m.p. 76° was confirmed as 6-nitrocholesta-4,6-diene (XCVIII) which was obtained by the loss of CH_3COOH from (XCVII). It is pertinent to mention that no α-acetylation occurred in (XLVI), but lead (IV) acetate promoted the elimination of acetic acid from (XLVI). Formation of 6-nitrocholesta-4,6-diene (XCVIII) can be explained assuming that the compound (XCVII), a α-acetylated product was first formed which eliminates acetic acid to provide (XCVIII) which on ketonization provides cholest-4-en-6-one (XCIX) a known ketone.

(C) Reaction of chlorotrimethylsilane with Bromo nitrosteroids

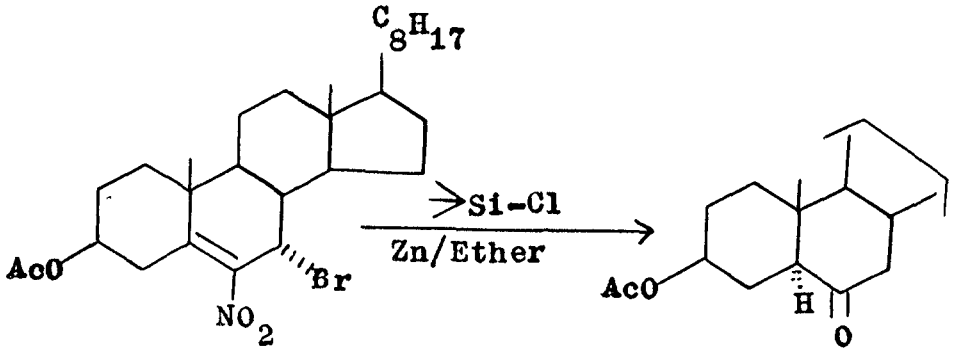
Recent publications[81-85] have highlighted diverse utility of chlorotrimethylsilane ($ClMe_3Si$) as an important reagent for organic synthesis. This reagent can be used either directly or in combination with a suitable metal. The versatile nature of chlorotrimethylsilane in chemical transformations prompted us to carry out the reaction 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII), 3β-chloro-7α-bromo-6-nitrocholest-5-ene (LXXXIX) and 4β,7α-dibromo-6-nitrocholest-5-ene (XC) with this reagent. Our study showed that chlorotrimethylsilane reduces the olefinic nitro group present in ring 'B' of steroid to ketone and debromination also took place from C7 and C4 positions.



	R	X
(LXXXVIII)	OAc	H
(LXXXIX)	Cl	H
(XC)	H	Br

Reaction of chlorotrimethylsilane with 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII)

Treatment of (LXXXVIII) with chlorotrimethylsilane and zinc dust at room temperature, gave a compound, m.p. 127°.



(LXXXVIII) (LXV)

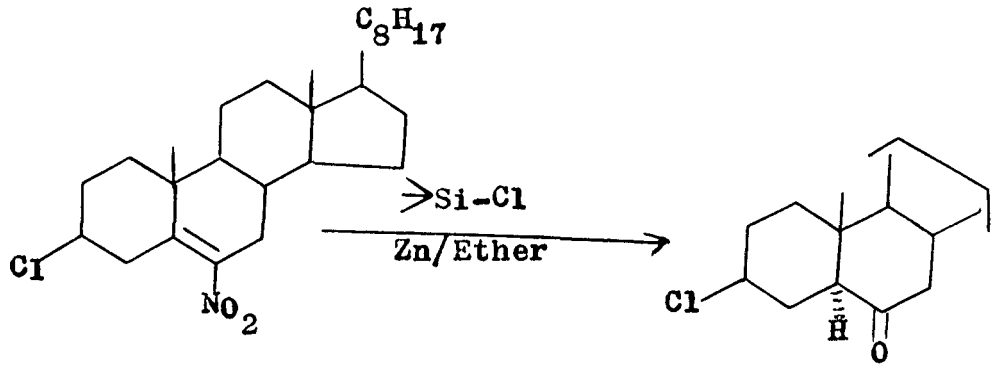
Characterization of the compound, m.p. 127° as 3β-acetoxy-5α-cholestan-6-one (LXV)

The compound, m.p. 127° was analysed for $C_{29}H_{48}O_3$. A negative Beilstein test showed that the bromine was lost from parent compound (LXXXVIII). I.R. spectrum of this compound displayed bands at 1722 (CH_3COO), 1711 (C=O) and 1235 cm^{-1} (C-O). Its N.M.R. spectrum gave a multiplet centred at δ 4.58 for C3-αH ($W\frac{1}{2}$ = 15 Hz; axial, A/B ring

junction trans). A sharp singlet at δ 1.98 for three protons is ascribable to C3-acetate protons ($C\underline{H}_3$-COO). Methyl protons were observed at δ 1.02 (C10-$C\underline{H}_3$), 0.60 (C13-$C\underline{H}_3$), 0.80 and 0.75 (remaining methyls). From the above data it was evident that the compound, m.p. 127° was 3β-acetoxy 5α-cholestan-6-one (LXV) which was further confirmed by comparison with its authentic sample prepared according to the literature procedure.[86]

Reaction of chlorotrimethylsilane with 3β-chloro-7α-bromo-6-nitrocholest-5-ene (LXXXIX)

Reaction of (LXXXIX) with chlorotrimethylsilane and zinc dust in usual way furnished a compound, m.p. 128°.



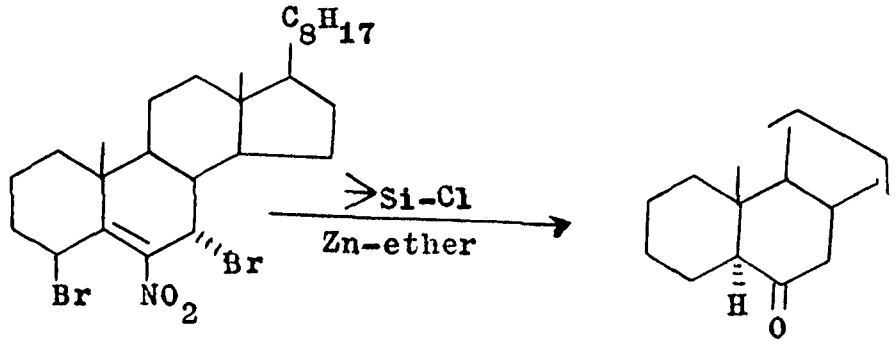
(LXXXIX) (C)

Characterization of the compound, m.p. 128° as 3β-chloro-5α-cholestan-6-one (C)

The compound, m.p. 128° was analysed for $C_{27}H_{45}OCl$. Its I.R. spectrum showed absorption bands at 1710 cm^{-1} (C=O) and 710 cm^{-1} (C-Cl). N.M.R. spectrum of this compound gave a multiplet centred at δ 3.69 for C3-α$\underline{H}$ ($W\frac{1}{2}$ = 12 Hz; axial; A/B ring junction trans). Methyl protons appeared at δ 1.26 (C10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$), 0.93 and 0.83 (remaining methyls). The compound, m.p. 128° was confirmed as 3β-chloro-5α-cholestan-6-one (C) by comparison with its authentic sample.[87]

Reaction of chlorotrimethylsilane with 4β,7α-dibromo-6-nitrocholest-5-ene (XC)

Treatment of (XC) with chlorotrimethylsilane and zinc dust in usual manner provided a compound, m.p. 98°.



(XC) (LXVII)

Characterization of the compound, m.p. 98° as 5α-cholestan-6-one (LXVII)

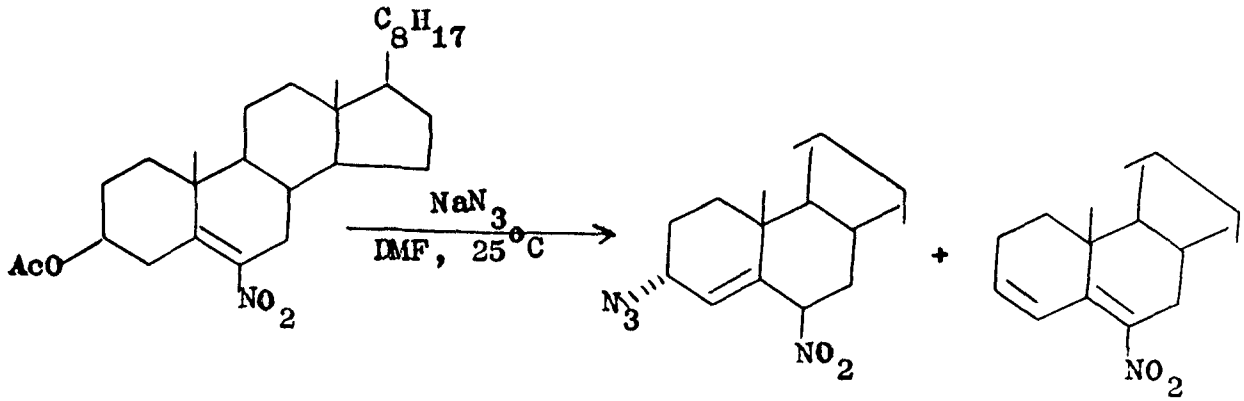
The compound, m.p. 98° was analysed for $C_{27}H_{46}O$ (negative Beilstein test). The molecular composition and Beilstein test showed that both bromine atoms were lost from the parent compound (XC). I.R. spectrum of this compound gave a strong absorption band at 1705 cm^{-1} for (C=O) group. N.M.R. spectrum showed a clean downfield. Methyl protons were seen at δ 1.20 (C10-CH_3), 0.68 (C13-CH_3), 0.90 and 0.80 (remaining methyl protons). The compound (LXVII) was found identical with the authentic sample of 5α-cholestan-6-one.[88]

(D) Synthesis and reactions of steroidal conjugated nitro olefins

Conjugated cyclic nitro olefins were reported versatile synthetic intermediate.[1] We have prepared 6-nitrocholesta-3,5-diene (XLVI) and studied some of the transformations with it.

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with sodium azide-DMF

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with sodium azide in DMF, afforded 6-nitrocholesta-3,5-diene (L) and a compound, m.p. 107°.



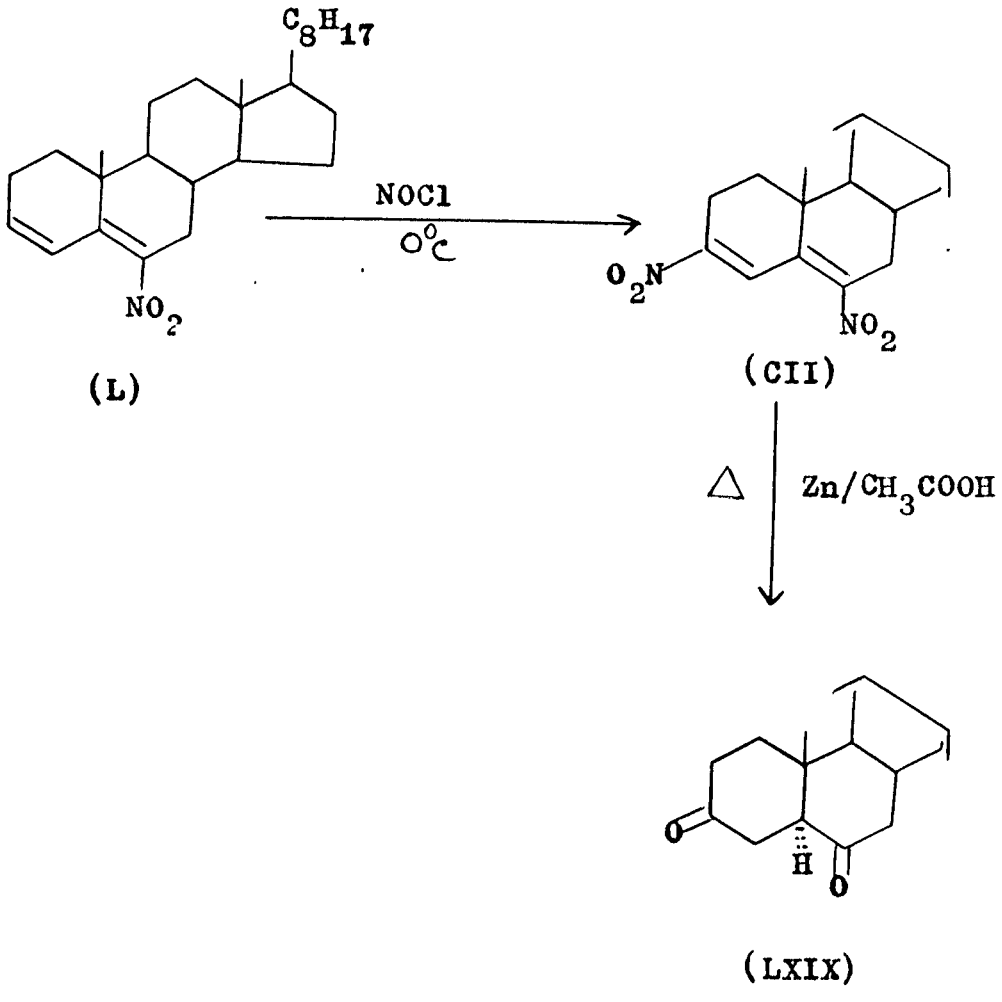
(XLVI) (CI) (L)

Characterization of the compound, m.p. 107° as 3α-azido-6-nitrocholest-4-ene (CI)

The compound, m.p. 107° was analysed for $C_{27}H_{44}N_4O_2$. From the composition it is evident that three nitrogen atoms were added to parent compound (XLVI). The band at 2120 cm^{-1} in I.R. spectrum suggests the presence of azide group. Other bands at 1660, 1540 and 1380 cm^{-1} were ascribable to (C=C) and ($C-NO_2$) stretching respectively. The $C-NO_2$ stretching at 1540 and 1380 cm^{-1} indicated that the NO_2 group attached to the saturated carbon.[26] Therefore double bond has been migrated from C6 to C4 which was supported by N.M.R. spectrum. N.M.R. spectrum revealed a broad singlet at δ 4.0 ($W_{\frac{1}{2}}$ = 4 Hz) integrating for one proton was ascribable to C3-β$\underline{H}$ (equatorial) therefore azido group at C-3 was axial (α) oriented. A doublet at δ 5.9 (J=2 Hz), was assigned to C4-$\underline{H}$ and a multiplet was observed at δ4.7 for C6-α$\underline{H}$ ($W_{\frac{1}{2}}$ = 4 Hz; equatorial). Methyl signals were obtained at δ1.50 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.76 and 0.91 (remaining methyl protons). On the basis of above elemental analysis and spectral evidences the compound, m.p. 107° was characterized as 3α-azido-6-nitrocholest-4-ene (CI).

Reaction of 6-nitrocholesta-3,5-diene (L) with nitrosyl chloride gas

6-Nitrocholesta-3,5-diene (XCVIII) was dissolved in carbon tetrachloride and cooled to $0^{o}C$. The nitrosyl chloride gas was passed directly into the solution for one hour. After usual work up and column chromatography over silica gel the reaction mixture afforded a compound, m.p. 113^{o}.

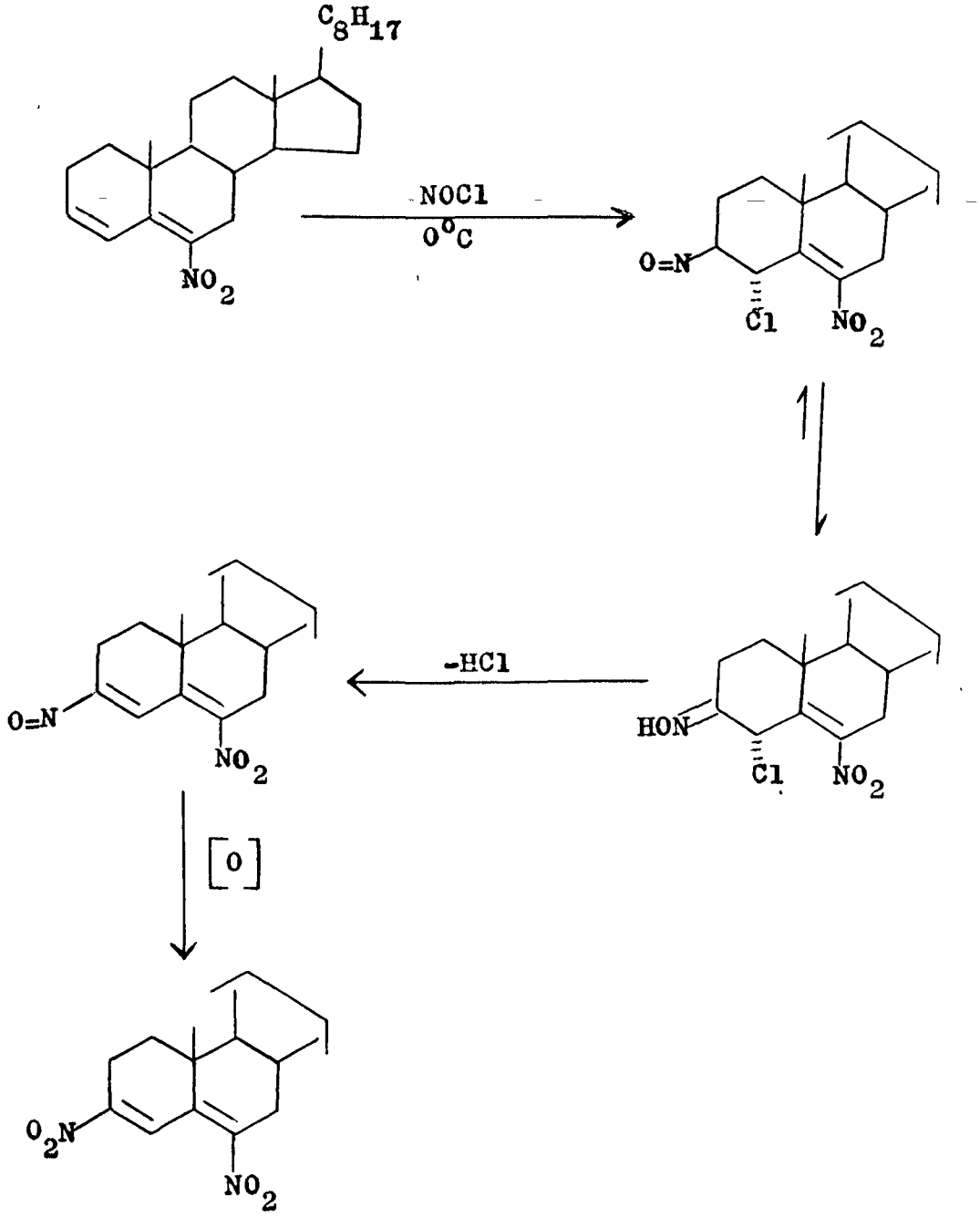


(LXIX)

Characterization of the compound, m.p. 113° as 3,6-dinitrocholesta-3,5-diene (CII)

The compound, m.p. 113° was analysed correctly for $C_{27}H_{42}N_2O_4$. From the composition it was evident that two oxygen atoms and one nitrogen atom were introduced to the substrate (L). In its I.R. spectrum strong absorption bands were seen at 1515, 1380 and 1651 cm^{-1} for $C-NO_2$ and C=C- stretching respectively. The N.M.R. spectrum exhibited a singlet at δ 7.68 for C4-proton. Angular methyl protons were observed at δ 1.10 (C10-CH_3), 0.71 (C13-CH_3), 0.94 and 0.83 (remaining methyl protons). From the above data it was evident that the compound, m.p. 113° may be 3,6-dinitrocholesta-3,5-diene (CII) which was further confirmed by its conversion to 5α-cholestan-3,6-dione (LXIX).[44] Formation of 3,6-dinitrocholesta-3,5-diene can be outlined according to Scheme - 4.

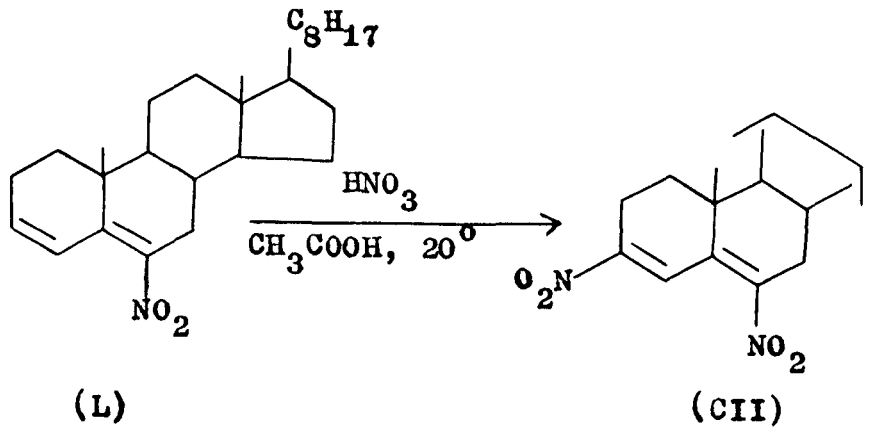
Scheme - 4



(CII)

Reaction of 6-nitrocholesta-3,5-diene (L) with HNO_3

Nitration of compound (L) with fuming nitric acid, sodium nitrite in glacial acetic acid below 20°, afforded a compound, m.p. 113°.



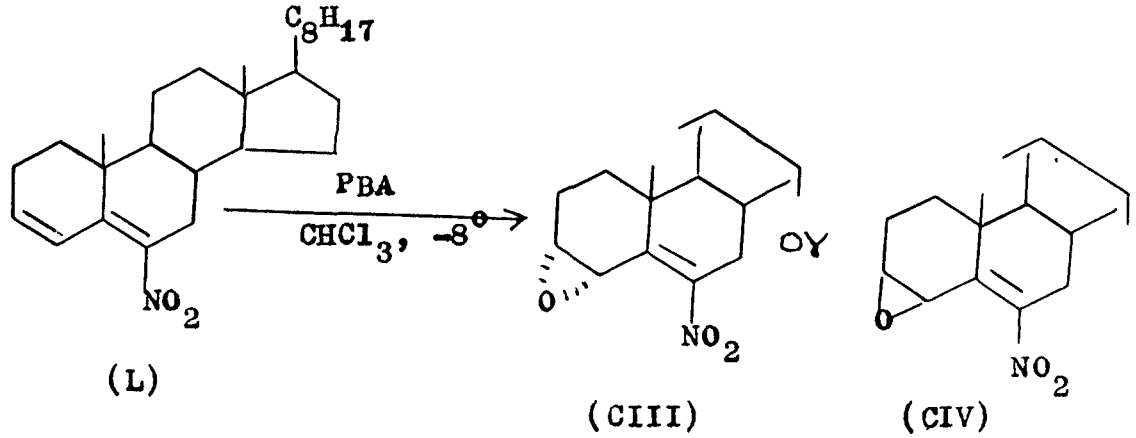
(L) (CII)

Characterization of the compound, m.p. 113° as 3,6-dinitrocholesta-3,5-diene (CII)

The compound, m.p. 113° was analysed for $C_{27}H_{42}N_2O_4$. This compound was found identical in all respects (m.p., t.l.c., i.r., n.m.r.) with (CII) which was obtained previously.

Reaction of 6-nitrocholesta-3,5-diene (L) with perbenzoic acid

The compound (L) was treated with perbenzoic acid (1.1 mole) in chloroform and left at -8°. The reaction mixture after usual work up provided a compound, m.p. 101°.



(L) (CIII) (CIV)

Characterization of the compound, m.p. 101° as 3α,4α-epoxy-6-nitrocholest-5-ene (CIII)

The compound, m.p. 101° showed the molecular composition $C_{27}H_{43}NO_3$, which indicated the addition of an oxygen atom to the substrate (L). The I.R. spectrum of compound m.p. 101° exhibited absorption bands at 1650, 1510, 1375 ($C-NO_2$), 1260 (epoxy ring)[89] and 1650 cm^{-1} (C=C). The N.M.R. spectrum of the compound showed a broad signal at δ 3.23 integrating for one proton with half band width 6 Hz

and was assigned to C3-proton. A doublet at δ 3.63 (J=3 Hz) was due to C4-proton. The J=3 Hz is suggestive of an interaction between equatorial and axial protons. The signal at δ 3.23 for C3-H with half band width 6 Hz implied that this proton is equatorial.[57] The presence of C3-H as equatorial (β-oriented) clearly indicated that C4-H is axial (β-oriented). Thus epoxide ring is α-oriented, therefore the epoxide structure is given as (CIII) α-epoxide and not as (CIV) β -oriented. The angular methyl protons signals were observed at δ 1.10 (C10-$\underline{CH}_3$), 0.70 (C13-$\underline{CH}_3$), 0.91 and 0.81 (other methyl protons). From these observations the compound, m.p. 101° may be regarded as 3α,4α-epoxy-6-nitrocholest-5-ene (CIII). The mass spectrum of compound (CIII)(Fig. 4) give the molecular ion peak at m/z 429 ($C_{27}H_{43}NO_3$) along with significant peaks at m/z 414 ($M^+ \cdot -CH_3$), 413 ($M^+ \cdot -O$), 412 ($M^+ \cdot -OH$), 383 ($M^+ \cdot -NO_2$), 372 ($M^+ \cdot -C_3H_5O$; base peak), 373 ($M^+ \cdot -C_3H_4O$), and other lower mass peaks. Formation of some of the fragment has been shown in Scheme-5 which is tentative in nature.

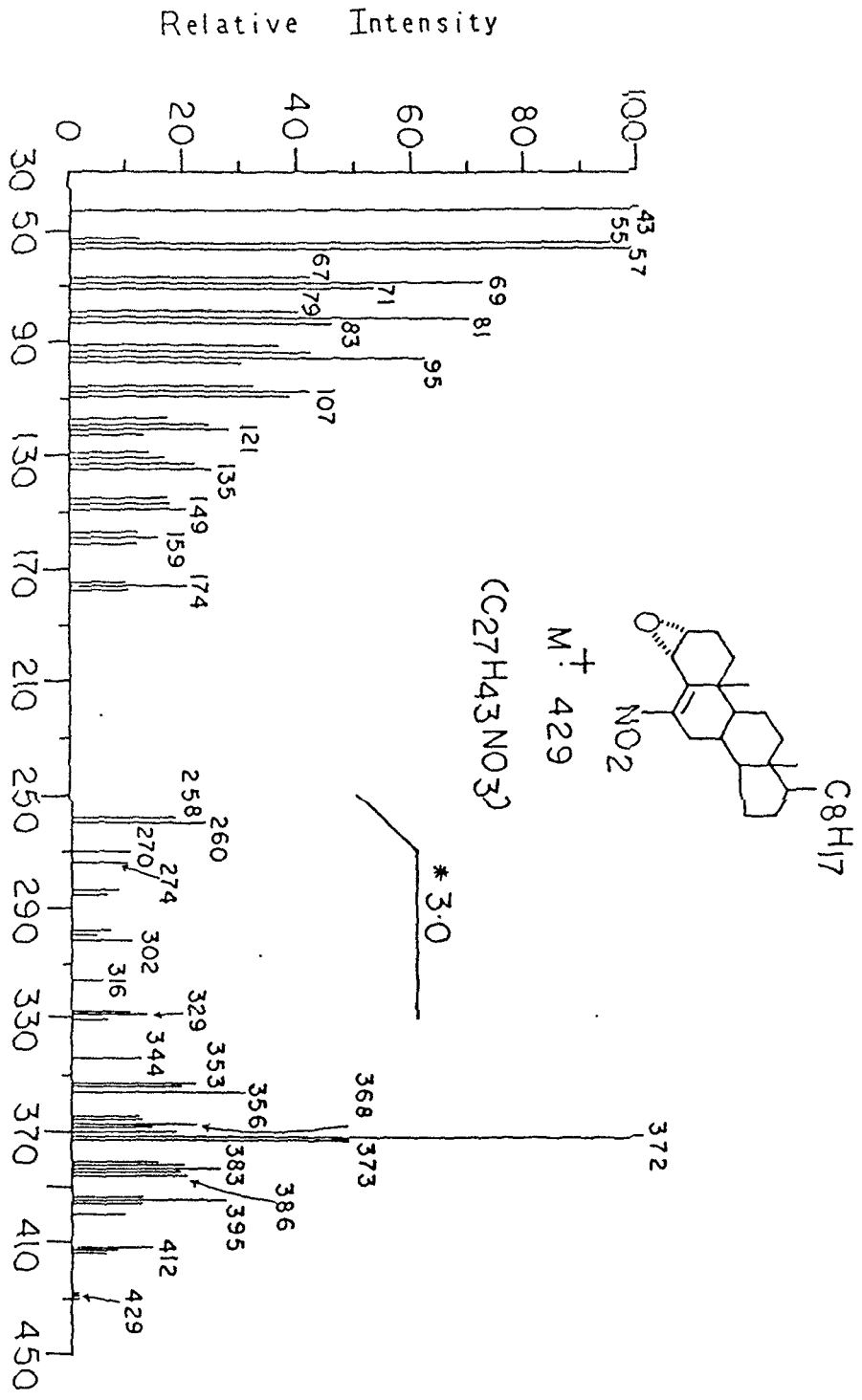
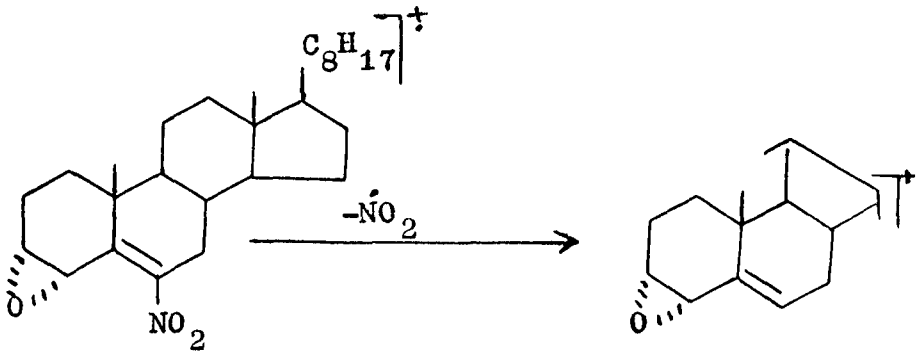


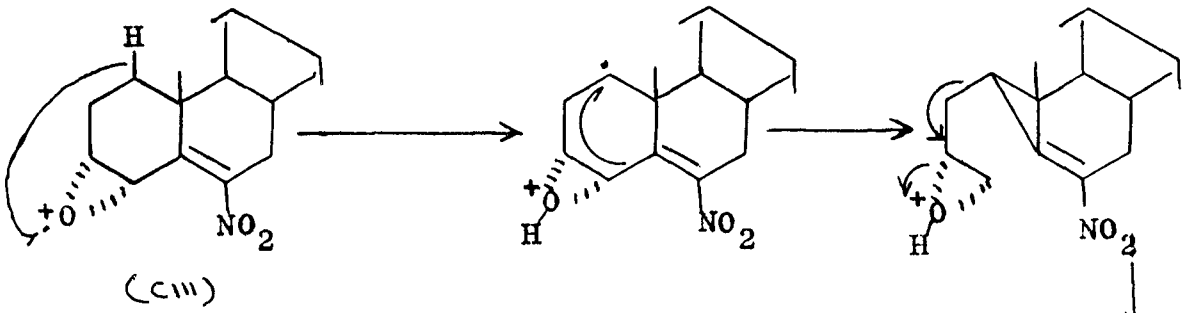
Fig. 4 Mass Spectrum of CIII.

Scheme - 5

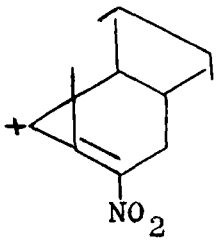


$M^+_{\bullet}$ 429
$(C_{27}H_{43}NO_3)$
(CIII)

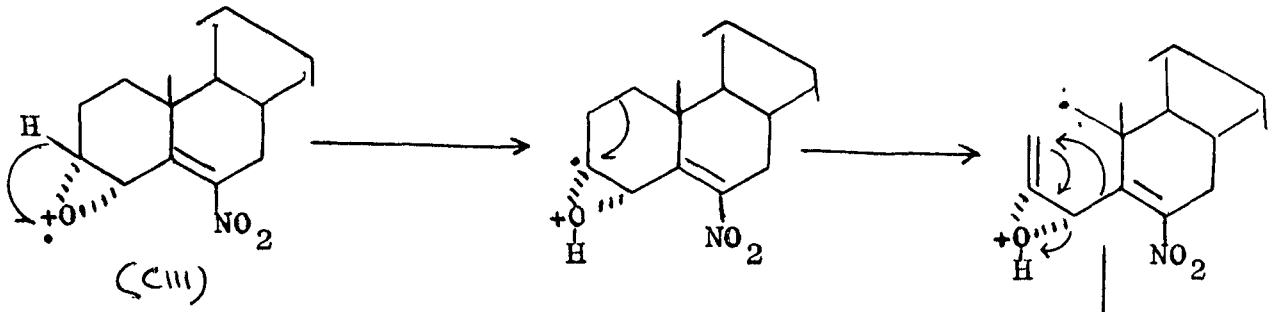
m/z 383
$(C_{27}H_{43}O)$



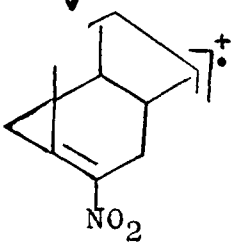
(CIII)



m/z 372
$(C_{24}H_{38}NO_2)$
base peak



(CIII)



m/z 373
$(C_{24}H_{30}NO_2)$

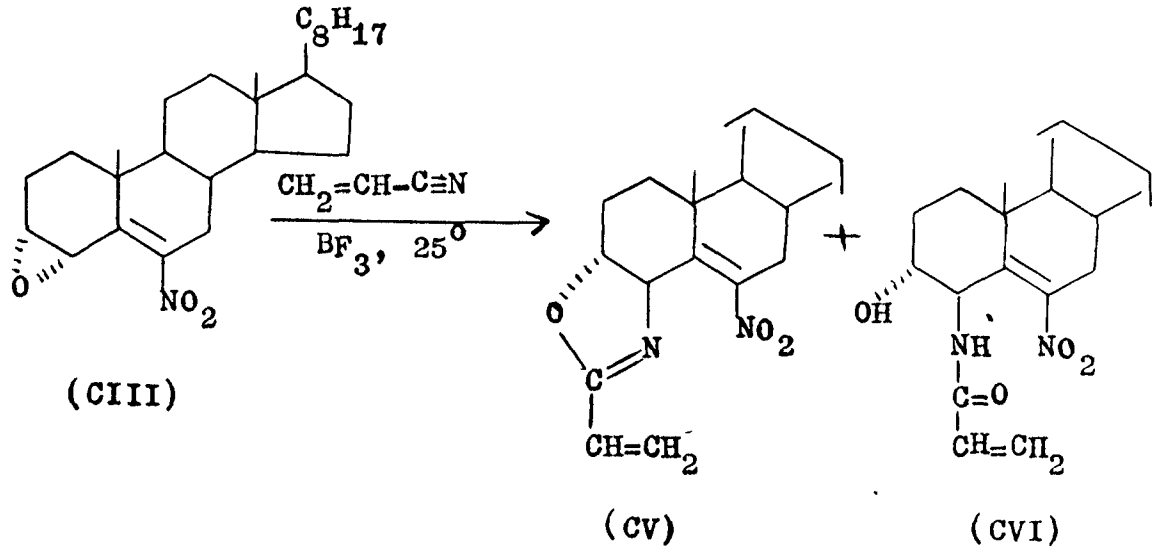
(E) Synthesis of steroidal oxazoline

Oxazolines have become of interest in recent years because of the discovery of the biological activities associated with these compounds and also because of their uses as potential drugs. As a result of this realization, synthesis of oxazolines become a matter of much interest and consequently a number of papers[90-97] appeared describing the preparation of oxazolines from various substrates.

The present work describes the preparation of oxazoline from epoxide (CIII).

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (CIII) with acrylonitrile-BF_3-etherate

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (CIII) with acrylonitrile in the presence of BF_3-etherate, afforded two compounds, m.p. 176° and 181°.



Characterization of the compound, m.p. 176° as 6-nitrocholest-5-eno [4β,3α-d]-2-vinyl-2-oxazoline (CV)

The compound, m.p. 176° was analysed for $C_{30}H_{46}N_2O_3$. Its I.R. spectrum gave bands at 1668 (C=N), 1620 (C=C), 1510 and 1370 ($C-NO_2$) and 1060 cm^{-1} (C-O-C). The N.M.R. spectrum displayed a multiplet at δ 3.93 ($W_{\frac{1}{2}}$ = 8 Hz), integrating for one proton, ascribable to C3-$\beta\underline{H}$. A doublet (J=4 Hz) at δ 4.55 was seen for C4-proton. The triplet at δ 5.63 and doublet (J=10 Hz) at δ 6.1 integrating for one and two protons were assigned to ($C\underline{H} = CH_2$) and ($CH = C\underline{H}_2$) respectively. Methyl protons were observed at δ 1.20 ($C10-C\underline{H}_3$), 0.70 ($C13-C\underline{H}_3$), 0.93 and 0.81 (other methyl protons). On the basis of foregoing discussion the compound m.p. 176° may be regarded as 6-nitrocholest-5-eno [4β,3α-d]-2-vinyl-2-oxazoline. Further evidence in support of this compound was given by its mass spectral study. The compound (CV) (Fig. 5) showed molecular ion peak at m/z 482 ($C_{30}H_{46}N_2O_3$). The other significant peaks were at m/z 465 (M^+-OH), m/z 450 (m/z 465-CH_3), m/z 437, m/z 436, ($M-NO_2$; base peak), m/z 435, ($M-HNO_2$), m/z 69 and lower mass peaks. The formation of these ions can be rationalized according to Scheme - 6 which is tentative in nature.

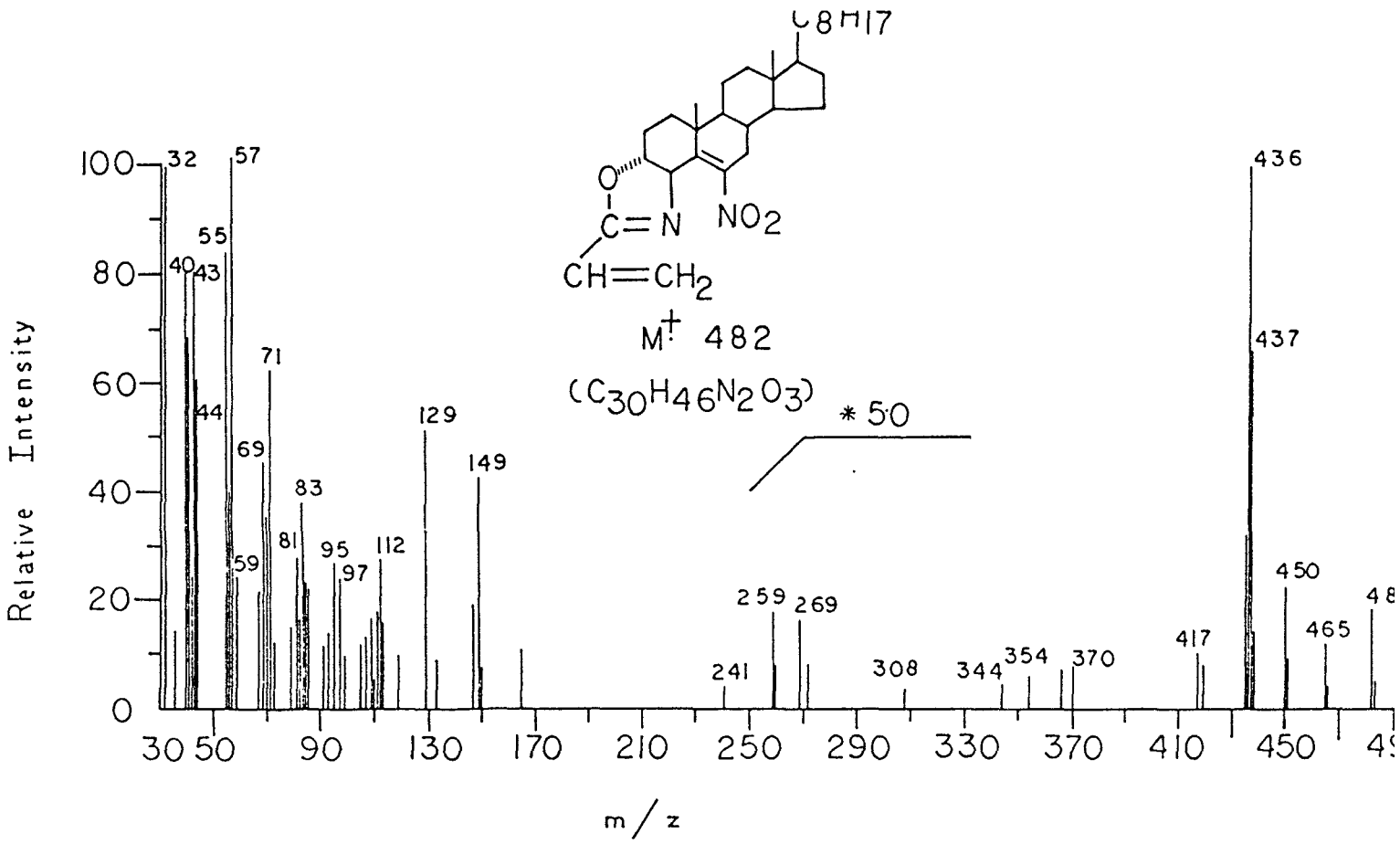
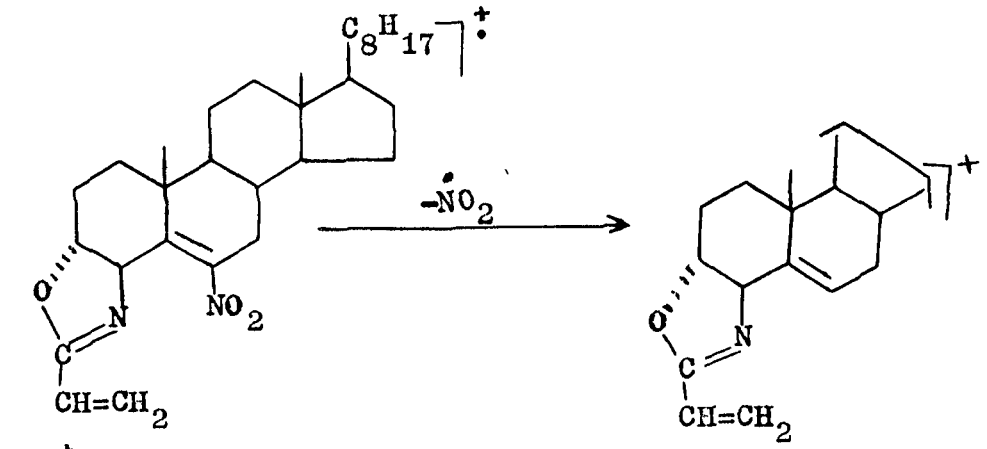


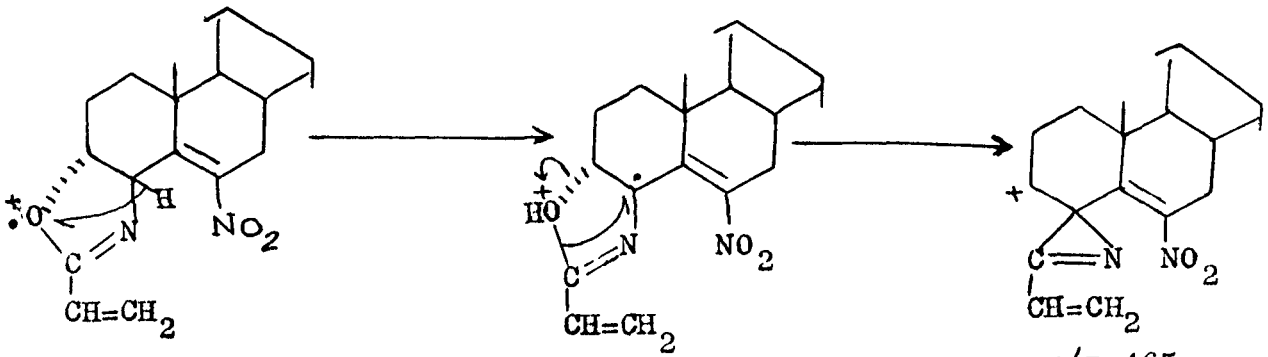
Fig. 5 Mass Spectrum of CV.

Scheme - 6

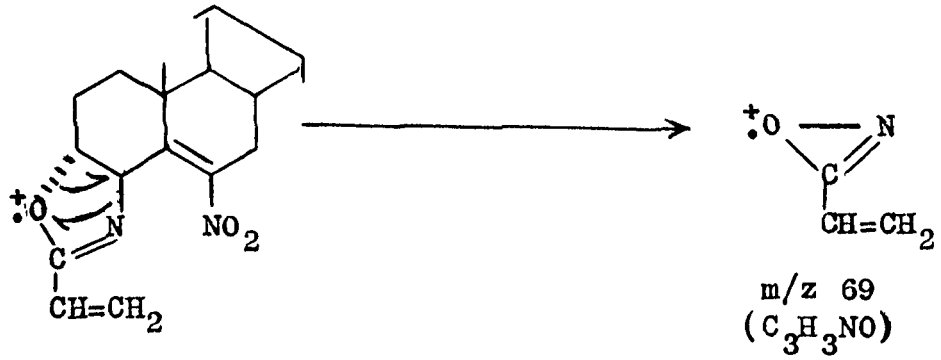


$M^{+\cdot}$ 482
($C_{30}H_{46}N_2O_3$)

m/z 436
($C_{30}H_{46}NO$)
(base peak)



m/z 465
($C_{30}H_{47}N_2O_2$)



m/z 69
(C_3H_3NO)

Characterization of the compound, m.p. 181° as 3α-hydroxy-6β-acrylamido-6-nitrocholest-5-ene (CVI)

The compound, m.p. 181° was analysed for $C_{30}H_{48}N_2O_4$. The I.R. spectrum showed bands at 3575 (-OH), 3200 (-NH), 1650 (amide I), 1510 (amide II), 1620 (C=C), 1510 and 1375 cm^{-1} (C-NO_2). In N.M.R. spectrum a broad signal appeared at δ 4.00 ($W\frac{1}{2}$ = 9 Hz) integrating for one proton which was assigned to (C3-βH; equatorial). A doublet (J=4 Hz) appeared at δ4.50 for (C4-α$\underline{H}$). A broad singlet at δ 6.50 (disappeared on addition of D_2O) integrating for one proton was assigned to (C4-N$\underline{H}$-C(=O)-). A doublet (J=10 Hz) for two protons appeared at δ 6.33 which was assigned to CH=C$\underline{H}_2$ and triplet was observed at δ 5.63 for C$\underline{H}$=CH_2. The 3α-hydroxy proton appeared as a broad signal at δ 4.50. Methyl signals were observed at δ 1.20 (C10-C$\underline{H}_3$), 0.70 (C13-C$\underline{H}_3$), 0.81 and 0.90 (remaining methyl protons). On the basis of above elemental and spectral data the compound (CVI) was characterized as 3α-hydroxy-6β-acrylamido-6-nitrocholest-5-ene which was further supported by its mass spectrum. The compound (CVI)(Fig. 6, Scheme - 7) showed the molecular ion peak at m/z 500 ($C_{30}H_{48}N_2O_4$). The other diagnostic peaks were at m/z 482 (M-H_2O), m/z 483 (M-OH), m/z 454 (M-NO_2; base peak), m/z 436 (m/z 454-H_2O), m/z 453 (M-HNO_2), m/z 399

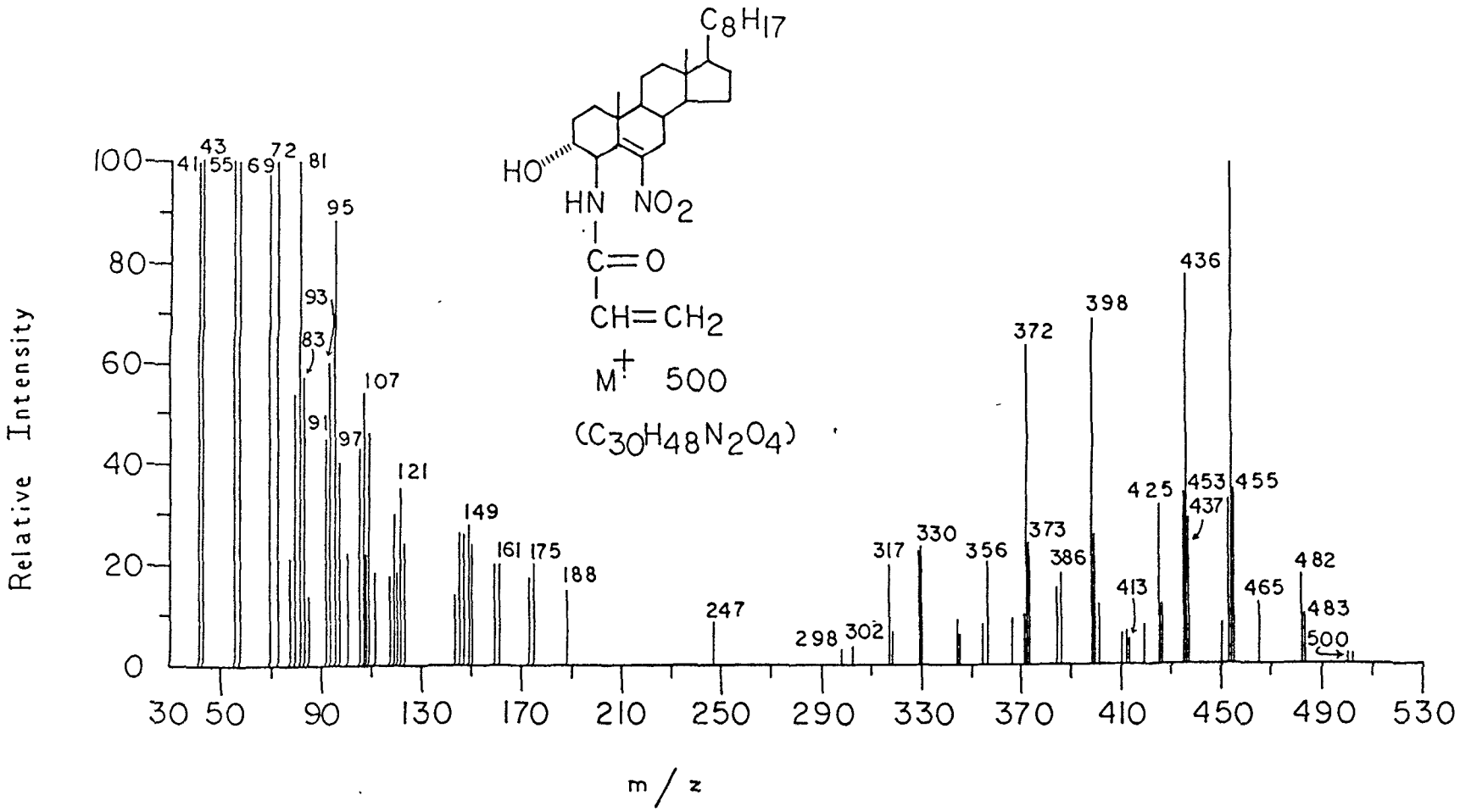
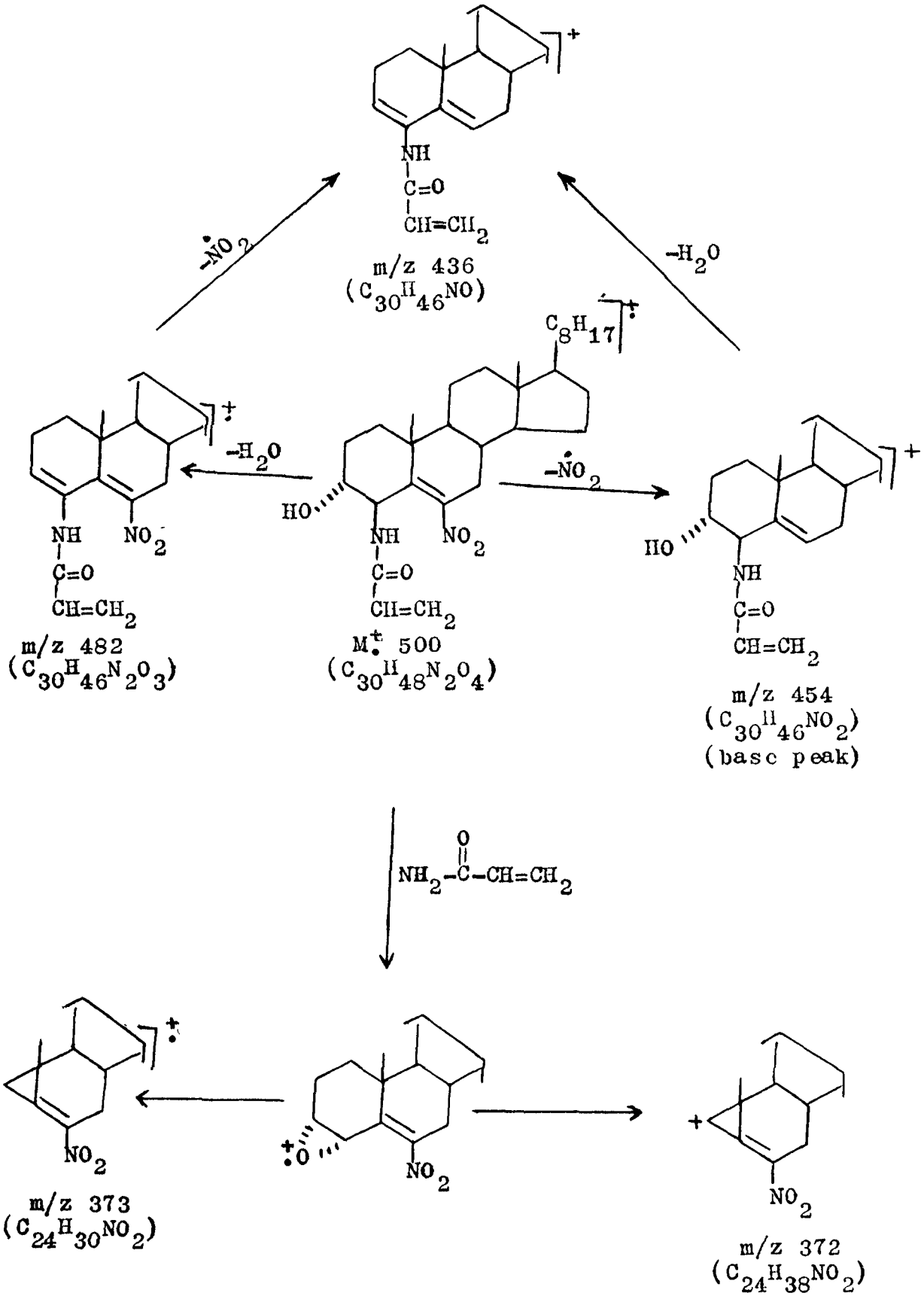


Fig. 6 Mass Spectrum of CVI.

(m/z 454-$COCH=CH_2$), m/z 398 (m/z 454-$COCH=CH_2$ + 1), m/z 373 (M-$C_6H_8NO_2$), m/z 372 (M-$C_6H_9NO_2$) and lower mass peaks.

Scheme - 7


NH
C=O
CH=CH2
m/z 436
(C30H46NO)
-NO2
-H2O
C8H17
HO
NO2
m/z 482
(C30H46N2O3)
M+ 500
(C30H48N2O4)
m/z 454
(C30H46NO2)
(base peak)
NH2-C(=O)-CH=CH2
m/z 373
(C24H30NO2)
m/z 372
(C24H38NO2)

Experimental

All melting points are uncorrected. I.R. spectra were determined in Nujol with Perkin-Elmer-237 and 621 spectrophotometers. N.M.R. spectra were run in $CDCl_3$ on a Varian A60 instrument with Me_4Si as the internal standard. Mass spectra were measured on a Jeol-D300 and JMSD-100 Mass spectrometers at 70 eV. CD curves were measured with a Jasco J-20 spectropolarimeter. TLC plates were coated with silica gel. A 20% aqueous solution of perchloric acid was used as spraying agent. Light petroleum refers to a fraction of b.p. 60-80°. N.M.R. values are given in ppm (s = singlet, d = doublet, t = triplet, br= broad, mc = multiplet centred at).

3β-Acetoxycholest-5-ene

A mixture of cholesterol (50.0 g), pyridine (75 ml, freshly distilled over KOH) and freshly distilled acetic anhydride (50 ml) was heated on a steam bath for 2 hours. The resulting brown solution was poured on to crushed ice-water mixture with stirring. A light brown solid was

obtained which was filtered under suction, washed with water until free from pyridine and air-dried. The crude product on recrystallization from acetone gave pure 3β-acetoxy cholest-5-ene (45.0 g), m.p. 114-115° (reported[80] m.p. 116°).

3β-Acetoxy-6-nitrocholest-5-ene (XLVI)

3β-Acetoxycholest-5-ene (10 g) was covered with nitric acid (d, 1.52; 250 ml) and sodium nitrite (10 g) was gradually added over a period of one hour with continuous stirring. Slight cooling was also required during the course of reaction. Stirring was continued for additional two hours. When a yellow spongy mass separated on the surface of the mixture, the mixture was diluted with cold water (250 ml). A green coloured solution was obtained. The whole mass was extracted with ether and washed successively with water, sodium bicarbonate solution (5%) and water. The ether solution was then dried over anhydrous sodium sulphate and filtered. Removal of the solvent provided an oil which was recrystallized from methanol to yield (XLVI), (6.8 g), m.p. 103° (reported[98] m.p. 102-104°).

Bromination of 3β-acetoxy-6-nitrocholest-5-ene (XLVI): 3β-Acetoxy, 7α-bromo-6-nitrocholest-5-ene (LXXXVIII)

To a solution of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) (5 g) in carbon tetrachloride (250 ml), N-bromo-succinimide (5 g) was added with few crystals of benzoyl peroxide as catalyst and refluxed for 3 hours. After cooling the insoluble succinimide was filtered off and the solvent was removed under reduced pressure. A dark brown residue thus obtained was chromatographed over silica gel (100 g). Elution with petroleum ether:ether (15:1) afforded 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII) as solid which was crystallized from petroleum ether (3.700 g), m.p. 165°. (Found: C, 63.01; H, 9.02; N, 2.50. $C_{29}H_{46}NO_4Br$ requires: C, 63.43; H, 8.33; N, 2.53%).

I.R. : $\nu_{max.}$ 1740 ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1240 (C-O), 1655 (C=C), 1515 and 1375 ($C-NO_2$), 675 cm^{-1} (C-Br).

N.M.R. : δ 4.67m (C3-αH), 5.08 br,s (C7-βH), 2.0s ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1.1 (C10-$CH_3$), 0.73 (C13-$CH_3$), 0.83 and 0.91 (remaining methyl protons).

MS : M^+ 551/553

C.D. : negative cotton effect (λ 254 nm).

Treatment of 3β-acetoxy,7α-bromo-6-nitrocholest-5-ene (LXXXVIII) with pyridine: 3β-Acetoxy-6-nitrocholesta-4,6-diene (XCI)

The compound (LXXXVIII) (1 g) was dissolved in (100 ml) pyridine and was heated under reflux for 2 hours. The reaction mixture was extracted with ether and ethereal solution was washed successively with water, dil-hydrochloric acid, water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was chromatographed over silica gel (20 g). Elution with petroleum ether: ether (10:1) afforded 3β-acetoxy-6-nitrocholesta-4,6-diene (XCI), recrystallized from petroleum ether (600 mg), m.p. 103°. (Found: C, 73.85; H, 9.49; N, 2.87. $C_{29}H_{45}NO_2$ requires: C, 73.88; H, 9.55; N, 2.98%).

I.R. ν max. 1730 ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1225 (C-O), 1615 (C=C), 1510 and 1370 cm^{-1} ($C-NO_2$).

N.M.R.: δ 5.33 (C3-$\underline{H}$), 6.43br,s (C7-$\underline{H}$), 5.72 br,s (C4-$\underline{H}$), 2.03s ($C\underline{H}_3-\underset{\underset{O}{\|}}{C}-O$), 1.05 (C10-$C\underline{H}_3$), 0.75 (C13-$C\underline{H}_3$), 0.83 and 0.91 (remaining methyl protons).

Treatment of 3β-acetoxy-6-nitrocholesta-4,6-diene (XCI) with Zn-AcOH: 3β-Acetoxycholest-4-en-6-one (XLIX)

To a solution of 3β-acetoxy-6-nitrocholesta-4,6-diene (XCI) (500 mg) in hot glacial acetic acid (15 ml), zinc power (1 g) was added gradually in small portions with shaking. The suspension was heated under reflux for 2 hours and water (1 ml) was added at regular intervals during the course of reaction. The hot solution was filtered and the filtrate was cooled to room temperature followed by dilution with ice-cooled water. The organic material was extracted with ether. Removal of the solvent furnished ketone (XLIX), crystallized from methanol (300 mg), m.p. 109° (reported[62] m.p. 110°).

3β-Chlorocholest-5-ene

Freshly purified thionyl chloride (75 ml) was gradually added to cholesterol (100 g) at room temperature. A vigorous reaction ensued with evolution of gaseous products. When the reaction slackened, the mixture was gently heated (50-60°) on a water bath for 1 hour, and then poured into crushed ice with stirring. The yellow solid mass thus obtained was filtered under suction and washed

several times with ice-cold water and air-dried. Recrystallization from acetone gave 3β-chlorocholest-5-ene (92.0 g), m.p. 95-96° (reported[99] m.p. 96-97°).

3β-Chloro-6-nitrocholest-5-ene (LXXIV)

To a well stirred mixture of 3β-chlorocholest-5-ene (10 g), glacial acetic acid (70 ml) and nitric acid (d, 1.52, 20 ml) cooled below 20°, sodium nitrite (5 g) was added gradually over a period of 2 hours. After the complete addition of sodium nitrite, the mixture was further stirred for 1 hour. Ice-cooled water (180 ml) was added and yellow solid was separated under suction, and air-dried. The product was crystallized from methanol as needles (7.0 g), m.p. 152° (reported[100] m.p. 153°).

Bromination of 3β-chloro-6-nitrocholest-5-ene (LXXIV): 3β-chloro,7α-bromo-6-nitrocholest-5-ene (LXXXIX)

3β-Chloro-6-nitrocholest-5-ene (LXXIV) (5 g) and N-bromosuccinimide (5 g) in carbon tetrachloride (250 ml), with a few crystals of benzoyl peroxide was refluxed for 3 hours. The reaction mixture was worked up in usual manner and chromatographed over a column of silica gel (100 g).

Elution with petroleum ether:ether (15:1) afforded (LXXXIX) which was recrystallized from petroleum ether (3.0 g), m.p. 167°. (Found: C, 60.60; H, 8.64; N, 2.59 ($C_{27}H_{43}NO_2BrCl$ requires: C, 61.3; H, 8.10; N, 2.64%).

I.R. : ν max. 1660 (C=C), 1515 and 1375 ($C-NO_2$), 760 (C-Cl), 665 cm^{-1} (C-Br).

N.M.R.: δ 4.0m (C3-$\alpha\underline{H}$), 5.12 br,s (C7-$\beta\underline{H}$), 1.20 (C10-$C\underline{H}_3$), 0.73 (C13-$C\underline{H}_3$), 0.83 and 0.93 (remaining methyl protons).

MS : :M^+ 527/529/531

C.D.: Negative cotton effect (λ 255 nm).

Treatment of 3β-chloro,7α-bromo-6-nitrocholest-5-ene (LXXXIX) with pyridine:6-Nitrocholesta-2,4,6-triene (XCII)

The bromo compound (LXXXIX) (1 g) was treated with pyridine (100 ml) under reflux for 1 hour. After usual work up it gave an oil which was chromatographed over a column of silica gel (20 g). Elution with petroleum ether-ether (15:1) gave 6-nitrocholesta-2,4,6-triene (XCII) as an oil (600 mg). (Found: C, 78.80; H, 9.45; N, 3.40. $C_{27}H_{41}NO_2$ requires: C, 78.83; H, 9.97; N, 3.46%).

I.R. : ν max. 1540 and 1390 ($=C-NO_2$) 1640 cm^{-1} (C=C-C=C-C=C-, NO_2).

N.M.R.: δ 5.9 (C7-$\underline{H}$), 6.2 to 7.0 br, mc (C2, C3, C4-$\underline{H}$), 1.05 (C10-$C\underline{H}_3$), 0.66 (C13-$C\underline{H}_3$), 0.83 and 0.93 (remaining methyl protons).

Treatment of 6-nitrocholesta-2,4,6-trien (XCII) with Zn-AcOH: Cholesta-2,4-dien-6-one (XCIII)

6-Nitrocholesta-2,4,6-triene (XCII) (500 mg) was dissolved in acetic acid (15 ml). To this, zinc powder (1 g) was added gradually in small portions with shaking. The suspension was refluxed for 2 hours and water (1 ml) was added at regular intervals. The reaction mixture was worked up in usual manner. Evaporation of the solvent and crystallization of the crude product (from methanol) gave (XCIII) (350 mg), m.p. 187° (reported[63] m.p. 187-188°).

Cholest-5-ene

3β-Chlorocholest-5-ene (12 g) was dissolved in warm amyl alcohol (280 ml) and sodium metal (24 g) was added in small pieces, to the solution with continuous stirring, over a period of 8 hours. The reaction mixture was warmed occasionally. When all the sodium metal dissolved, the reaction mixture was poured into 5% hydrochloric acid (600 ml) and then allowed to stand overnight at room temperature. White crystalline solid thus obtained was filtered and washed thoroughly with water and dried in air. The crude product was crystallized from acetone, in needle shaped crystals (9.5 g), m.p. 90° (reported[101] m.p. 89.5-91.2).

6-Nitrocholest-5-ene (LXXV)

A suspension of freshly powdered cholest-5-ene (12 g) in glacial acetic acid (100 ml) was vigorously stirred at room temperature and treated with nitric acid (d, 1.52, 30 ml), followed by addition of sodium nitrite (3 g) over a period of 2 hours. The reaction mixture was poured into ice-cold water and the yellow product obtained was extracted with ether. Usual work up and removal of the solvent provided the desired compound (LXXV) as an oil, which was crystallized from ethanol (8.5 g), m.p. 119-120° (reported[102] m.p. 120-121°).

Bromination of 6-nitrocholest-5-ene (LXXV):4β,7α-Dibromo-6-nitrocholest-5-ene (XC)

6-Nitrocholest-5-ene (LXXV) (5 g) with N-bromosuccinimide (5 g) in carbon tetrachloride was refluxed in manner described for the previous reaction. Work up of the reaction mixture followed by evaporation of the solvent yielded a brown residue which was chromatographed over silica gel (100 g). Elution with petroleum ether:ether (15:1) afforded 4β,7α-dibromo-6-nitrocholest-5-ene (XC) (2.0 g) m.p. 143° (Found: C, 56.10; H, 7.83; N, 2.40. $C_{27}H_{43}NO_2Br_2$ requires: C, 56.54; H, 7.50; N, 2.44%).

I.R. : ν max 1625 (C=C), 1525 and 1375 ($C-NO_2$), 612 cm^{-1} (C-Br).

N.M.R.: δ 5.56 br,s (C4-$\alpha\underline{H}$), 5.05 br,s (C7-$\beta\underline{H}$), 1.55s (C10-$C\underline{H}_3$), 0.71 (C13-$C\underline{H}_3$), 0.83 and 0.91 (remaining methyl protons).

MS : m/z 492/494 (M^+ -Br).

Reaction of 3β-chloro-6-nitrocholest-5-ene (LXXIV) with $Pb(OAc)_4$: 3β-Chloro-7α-acetoxy-6-nitrocholest-5-ene (XCIV), 3β-chloro-5,6α-diacetoxy-6-nitro-5α-cholestane (XCV) and 3β-chloro-4β,7α-diacetoxy-6-nitrocholest-5-ene (XCVI)

The mixture of 3β-chloro-6-nitrocholest-5-ene (LXXIV) (2 g), lead (IV) acetate (4 g), anhydrous potassium acetate (1 g) was refluxed in glacial acetic acid (150 ml) for 12 hours. The reaction mixture was cooled to room temperature, diluted with ice-cold water, and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution (5%) and water and dried over sodium sulphate anhydrous. Evaporation of the solvent gave a residue which was chromatographed over silica gel (40 g). Elution with light petroleum ether: ether (20:1) furnished an oil (XCIV) (Found: C, 78.35; H, 10.30; N, 3.38; $C_{29}H_{46}NO_4Cl$ requires: C, 78.45; H, 10.41; N, 3.28%).

I.R. : ν max. 1745 ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1270-1210 (C-O), 1630 (C=C), 1510 and 1365 ($C-NO_2$), 710 cm^{-1} (C-Cl).

N.M.R. : δ 5.65 br,s (C7-$\beta\underline{H}$), 3.50 mc (C3-$\alpha\underline{H}$; $W\frac{1}{2}$ = 18 Hz), 2.01s ($C\underline{H}_3-\underset{\underset{O}{\|}}{C}-O$), 1.15 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.81 and 0.90 (remaining methyl protons).

Further elution with petroleum ether:ether (16:1) gave an oil (XCV) (700 mg) (Found: C, 65.40; H, 8.70; N, 2.43; $C_{31}H_{50}NO_6Cl$ requires: C, 65.49; H, 8.79; N, 2.46%).

I.R. : ν max. 1730 ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1280-1220 (C-O), 1510 and 1365 ($C-NO_2$), 715 cm^{-1} (C-Cl).

N.M.R. : δ 1.96 with two notches at 2.0 and 1.93 (2 x $C\underline{H}_3-\underset{\underset{O}{\|}}{C}-O$), 4.10 mc (C3-$\alpha\underline{H}$; $W\frac{1}{2}$ = 18 Hz), 1.16 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.81 and 0.93 (remaining methyl protons).

Continued elution with light petroleum ether:ether (18:1) gave an oil (XCVI) (500 mg), (Found: C, 65.50; H, 8.43; N, 2.43. $C_{31}H_{48}NO_6Cl$ requires: C, 65.54; H, 8.45; N, 2.46%).

I.R. : ν max. 1730 ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1280-1230 (C-O), 1510 and 1370 ($C-NO_2$), 1645 (C=C), 740 cm^{-1} (C-Cl).

N.M.R. : δ 7.56d (C4-$\alpha\underline{H}$; J=3 Hz); 4.50 br,s (C7-$\beta\underline{H}$), 4.26 br,s (C3-$\alpha\underline{H}$; $W\frac{1}{2}$ = 8 Hz), 2.03 with two notches at δ 1.96 and 2.10 (2 x $C\underline{H}_3-\underset{\underset{O}{\|}}{C}-O$), 1.26 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.85 and 0.95 (remaining methyl protons).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with $Pb(OAc)_4$: 6-Nitrocholesta-3,5-diene (L)

3β-Acetoxy-6-nitrocholest-5-ene (XLVI) (5 g) was dissolved in acetic acid (150 ml) and (2 g) of anhydrous potassium acetate was added followed by the addition of (8 g) of lead tetraacetate. The mixture was refluxed for 12 hours in anhydrous condition. After the completion of reaction the reaction mixture was diluted by water and the compound extracted from ether. The ethereal layer was washed by water, sodium bicarbonate solution (5%) and water successively and dried over anhydrous sodium sulphate. The removal of the solvent gave an oil which was chromatographed over silica gel (100 g). Elution with light petroleum gave the unreacted compound (XLVI) and further elution with light petroleum ether:ether (20:1) gave a solid compound (L) recrystallized from methanol (4 g), m.p. 72° (reported[15] m.p. 72-73°) (Found: C, 78.42; H, 10.21; N, 3.35. $C_{27}H_{43}NO_2$ requires: C, 78.45; H, 10.41; N, 3.38%).

I.R. : ν_{max}. 1680 ($-C=C-C=C-NO_2$), 1508 and 1360 cm^{-1} ($C-NO_2$).

N.M.R. : δ 6.5d (C4-H; J=10 Hz), 6.1m (C3-H), 1.0 ($C10-CH_3$), 0.70 ($C13-CH_3$), 0.95 and 0.83 (remaining methyl protons).

MS : M^+ 413.

Reaction of 6-nitrocholest-5-ene (LXXV) with $Pb(OAc)_4$: 6-Nitrocholesta-4,6-diene (XCVIII)

The compound (LXXV) (5 g) was treated with lead tetraacetate in the usual manner. The reaction mixture after work up was chromatographed over silica gel (100 g). Elution with petroleum ether:ether (18:1) yielded (XCVIII) which was crystallized from methanol, (4 g), m.p. 76°. (Found: C, 78.43; H, 10.34; N, 3.36. $C_{27}H_{43}NO_2$ requires: C, 78.45; H, 10.41; N, 3.38%).

I.R. : ν max. 1680 ($C=C-C=C-NO_2$), 1515 and 1365 cm^{-1} ($C-NO_2$).

N.M.R.: δ 5.30 br,s (C7-$\underline{H}$), 5.75m (C4-$\underline{H}$), 1.21 (C10-C$\underline{H}_3$), 0.73 (C13-C$\underline{H}_3$), 0.86 and 1.0 (remaining methyl protons).

Treatment of 6-nitrocholesta-4,6-diene (XCVIII) with Zn-AcOH:Cholest-4-en-6-one (XCIX)

6-Nitrocholesta-4,6-diene (XCVIII) (1 g) was treated with zinc dust (4 g) and acetic acid (25 ml) in the manner described for the compound (XCII). Work up of the reaction mixture followed by evaporation of the solvent and subsequent crystallization from alcohol, yielded cholest-4-en-6-one (XCIX) (700 mg), m.p. 107° (reported[63] m.p. 107-108°).

Reaction of chlorotrimethylsilane and zinc dust with 3β-acetoxy,7α-bromo-6-nitrocholest-5-ene (LXXXVIII): 3βAcetoxy-5α-cholestan-6-one (LXV)

To a solution of 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (LXXXVIII) (2 g) in ether (100 ml) was added chlorotrimethylsilane (10 ml). To this mixture, zinc dust (6 g) was added in small portions over a period of 30 minutes. The reaction mixture was allowed to stand for 4 hours at room temperature (The progress of the reaction was checked through TLC). At the completion of reaction, zinc dust was filtered off and the solution was washed successively with water, sodium bicarbonate solution (2%) and water. Ether layer was dried over anhydrous sodium sulphate. Evaporation of the solvent gave 3β-acetoxy-5α-cholestan-6-one (LXV) which was crystallized from alcohol (1.70 g), m.p. 127° (reported[86] m.p. 127°).

Reaction of chlorotrimethylsilane and zinc dust with 3β-chloro,7α-bromo-6-nitrocholest-5-ene (LXXIX): 3β-Chloro-5α-cholestan-6-one (C)

To a solution of 3β-chloro,7α-bromo-6-nitrocholest-5-ene (LXXXIX) (2 g) in ether (120 ml) was added chlorotrimethylsilane (10 ml). To this mixture, zinc dust (6 g)

was added in small portions over a period of 30 minutes. The reaction mixture was allowed to stand for 4 hours at room temperature. At the completion of reaction, zinc dust was filtered off. The ether solution was worked up according to previous method. Evaporation of the solvent provided 3β-chloro-5α-cholestan-6-one (C). The ketone was crystallized from ethyl alcohol (1.75 g), m.p. 128° (reported[87], m.p. 129°).

Reaction of chlorotrimethylsilane and zinc dust with 4β,7α-dibromo-6-nitrocholest-5-ene (XC): 5α-Cholestan-6-one (LXVII)

4β,7α-Dibromo-6-nitrocholest-5-ene (XC) (2 g) was treated with chlorotrimethylsilane (10 ml) and zinc dust (8 g) in the manner described for the previous reaction. Work up of the reaction mixture, followed by evaporation of the solvent and subsequent crystallization from ethyl-alcohol yielded 5α-cholestan-6-one (LXVII) (1.27 g), m.p. 97° (reported[88] m.p. 98°).

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (XLVI) with NaN_3-DMF: 6-Nitrocholesta-3,5-diene (L) and 3α-azido-6-nitrocholest-4-ene (CI)

3β-Acetoxy-6-nitrocholest-5-ene (XLVI) (5 g) was dissolved in N,N-dimethyl formamide (20 ml), and sodium azide

(3 g) was added gradually with shaking. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%) and dried over sodium sulphate anhydrous. Removal of the solvent gave an oil which was chromatographed over silica gel (100 g). Elution with light petroleum ether:ether (20:1) furnished an oil (L) which was crystallized from methanol (4 g), m.p. 72° (reported[15] m.p. 72-73°).

Further elution with petroleum ether:ether (18:1) gave a compound (CI) crystallized from ethyl alcohol (500 mg), m.p. 107° (Found: C, 71.01; H, 9.60; N, 10.05, $C_{27}H_{44}N_4O_2$ requires: C, 71.05; H, 9.63; N, 10.08%).

I.R. : ν max. 2120 ($-N_3$), 1660 (C=C), 1540 and 1380 cm^{-1} ($C-NO_2$).

N.M.R.: δ 5.9d (C4-$\underline{H}$; J=2 Hz), 4.0br,s (C3-$\underline{\beta H}$; $W\frac{1}{2}$ = 4 Hz), 4.7m (C6-$\underline{\alpha H}$), 1.5 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.76 and 0.91 (remaining methyl protons).

Reaction of 6-nitrocholesta-3,5-diene (L) with Nitrosylchloride gas: 3,6-Dinitrocholesta-3,5-diene (CII)

6-Nitrocholesta-3,5-diene (L) (2 g) was dissolved in carbon tetrachloride and kept in the ice-salt mixture. The nitrosylchloride gas was passed in the solution for one hour. After the completion of reaction the solvent was removed under reduced pressure. A dark orange coloured residue thus obtained, was taken in ether. The ethereal solution was washed successively with water, sodium bicarbonate solution (1%) and water and dried over sodium sulphate (anhydrous). Removal of the solvent gave an oil (CII) crystallized from methanol (1.75 g), m.p. 113° (Found: C, 70.70; H, 9.15; N, 6.10. $C_{27}H_{42}N_2O_4$ requires: C, 70.74; H, 9.17; N, 6.11%).

I.R. : ν max. 1651 (C=C), 1515 and 1380 cm^{-1} ($C-NO_2$).

N.M.R.: δ 7.6 br,s (C4-$\underline{H}$), 1.10 (C10-$C\underline{H}_3$), 0.71 (C13-$C\underline{H}_3$), 0.83 and 0.94 (remaining methyl protons).

Reaction of 6-nitrocholesta-3,5-diene (L) with Nitric acid: 3,5-Dinitrocholesta-3,5-diene (CII)

To a well stirred mixture of 6-nitrocholesta-3,5-diene (L) (3 g), glacial acetic acid (25 ml) and nitric acid (10 ml, d, 1.52) at temperature below 20°, was added

sodium nitrite (1.5 g) gradually over a period of 2 hours. After complete addition of sodium nitrite, the mixture was further stirred for 1 hour. The reaction mixture was then poured into ice-cooled water. A yellow solid thus obtained, was taken in the ether. The solution was washed with water, sodium bicarbonate solution (5%) and water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was chromatographed over silica gel (40 g). Elution with light petroleum ether:ether gave compound (CII) crystallized from ethanol (1.60 g), m.p. 113° identical in all respects with previously obtained 3,6-dinitrocholesta-3,5-diene (CII).

Treatment of 3,6-dinitrocholesta-3,5-diene (CII) with Zn-AcOH:5α-Cholestan-3,6-dione (LXIX)

3,6-Dinitrocholesta-3,5-diene (CII) (500 mg) was treated with Zn dust (2 g) and acetic acid (20 ml) in the manner described for the previous reaction with (XCIX). Work up of the reaction mixture followed by evaporation of the solvent and subsequent crystallization from alcohol provided (LXIX) (350 mg), m.p. 168° (reported[44] m.p. 167-168°).

Reaction of 6-nitrocholesta-3,5-diene (L) with perbenzoic acid: 3α,4α-Epoxy-6-nitrocholest-5-ene (CIII)

6-Nitrocholesta-3,5-diene (L) (4 g) in chloroform (35 ml) was treated with solution of perbenzoic acid (1.1 mole) in chloroform and left at -8^{o} for 24 hours. The mixture was then washed with ice-cold sodium bicarbonate solution (5%), water and sodium thiosulphate solution (5%). Removal of the solvent gave (CIII) as an oil, crystallized from petroleum ether (3 g), m.p. 101^{o}. (Found: C, 75.49; H, 10.00; N, 3.24. $C_{27}H_{43}NO_3$ requires: C, 75.52; H, 10.02; N, 3.26%).

I.R. : ν max. 1260 (C$\overset{O}{\diagup\diagdown}$C), 1650 (C=C), 1510 and 1375 cm^{-1} ($C-NO_2$).

N.M.R.: δ 3.23 br,m (C3-βH; $W_{\frac{1}{2}}$ = 6 Hz), 3.63 d (C4-βH, J=3 Hz), 1.05 (C10-CH_3), 0.70 (C13-CH_3), 0.81 and 0.91 (remaining methyl protons).

MS : M^{+} 429.

Reaction of 6-nitrocholesta-3,5-diene (L) with m-chloroperbenzoic acid: 3α,4α-Epoxy-6-nitrocholest-5-ene (CIII)

6-Nitrocholesta-3,5-diene (L) (4 g) in chloroform (35 ml) was treated with m-chloroperbenzoic acid (1.80 g) in the manner described for previous reaction. The reaction mixture was worked up in usual manner. Evaporation of the solvent and subsequent crystallization from petroleum ether gave (CIII) (3.5 g), m.p. 101° (identical in all respects with previously obtained 3α,4α-epoxy-6-nitrocholest-5-ene (CIII)).

Reaction of 3α,4α-epoxy-6-nitrocholest-5-ene (CIII) with acrylonitrile: 3,6-Nitrocholest-5-eno [4β,3α-d]-2-vinyl-2-oxazoline (CV) and 3α-hydroxy 4β-acrylamido-6-nitrocholest-5-ene (CVI)

Borontrifluoride-etherate (2 ml) was added dropwise (in 15 minutes) to a stirred suspension of epoxide (CIII) (2 g) in acrylonitrile (20 ml) at room temperature. The resulting solution was further stirred for 20 minutes. The reaction mixture was poured into aqueous sodium bicarbonate solution and dichloromethane extract was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent gave an oil which was chromatographed over silica

gel (40 g). Elution with petroleum ether:ether (5:1) afforded (CV) crystallized from methanol (1.3 g), m.p. 176°. (Found: C, 74.60; H, 9.50; N, 5.76. $C_{30}H_{46}N_2O_3$ requires: C, 74.68; H, 9.54; N, 5.80%).

I.R. : ν max. 1668 (C=N), 1620 (C=C), 1510 and 1370 ($C-NO_2$), 1060 cm^{-1} (C-O-C).

N.M.R.: δ 3.93m (C3-$\beta\underline{H}$, $W\frac{1}{2}$ = 8 Hz), 4.55d (C4-$\alpha\underline{H}$), 5.63t ($-C\underline{H}=CH_2$), 6.1d ($-CH=C\underline{H}_2$), 1.20 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.81 and 0.93 (remaining methyl protons).

MS : M^+ 482.

Further elution with petroleum ether:ether (2:1) gave a compound (CVI) crystallized from methanol (500mg), m.p. 181°. (Found: C, 71.85; H, 9.58; N, 5.58. $C_{30}H_{48}N_2O_4$ requires: C, 72.01; H, 9.00; N, 5.60%).

I.R. : ν max. 3575 (OH), 3200 (NH), 1650, 1510 (amide I and II), 1620 (C=C), 1510 and 1375 cm^{-1} ($C-NO_2$).

N.M.R.: δ 4.00 mc (C3-$\beta\underline{H}$; $W\frac{1}{2}$ = 9 Hz), 4.20 br,s (OH), 4.50 d (C4-$\alpha\underline{H}$), 5.63t ($-C\underline{H}=CH_2$), 6.33d ($-CH=C\underline{H}_2$), 6.50 br,s (N$\underline{H}$), 1.20 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.81 and 0.90 (remaining methyl protons).

MS : M^+ 500.

The mass spectra were measured on a Varian Jeol-D300 and JMSD-100 mass spectrometers at 70 eV using a direct insertion technique at source temperature of about 250°C.

The value (m/z) of the fragment ions from various compounds were tabulated below. The value in parentheses are the relative abundance (%) of the peaks with respect to base peak as 100%.

3β-Acetoxy,7α-bromo-6-nitrocholest-5-ene (LXXXVIII)

M^{+} 551/553 (9.00; $C_{29}H_{46}NO_4Br$), m/z 507 (7.00), 4.93 (9.00), 491 (9.00), 471 (11.00), 457 (14.00), 456 (27.00), 426 (17.50), 425 (6.00), 413 (26.50), 412 (91.00), 411 (100), 396 (18.50), 395 (30.00), 384 (14.00), 383 (21.00), 380 (9.00), 379 (14.00), 378 (33.50), 370 (9.00), 369 (9.00), 368 (19.00), 367 (19.30), 366 (18.20), 365 (19.30), 298 (9.10), 282 (9.10), 247 (21.50), 203 (25.0), 179 (12.00), 177 (14.00), 173 (9.10), 172 (9.00), 161 (9.20), 160 (11.00), 158 (31.00), 157 (9.20), 149 (14.20), 147 (11.00), 143 (11.00), 135 (19.00), 134 (9.00), 133 (14.00), 131 (11.00), 123 (9.00), 121 (15.00), 119 (12.00), 110 (26.00), 108 (19.00), 96 (35.20), 84 (19.00), 83 (26.50), 82 (26.50), 80 (33.00), 71 (35.00), 69 (42.50), 60 (18.00), 57 (35.00), 55 (8.00), 45 (15.20), 43 (42.00).

3β-Chloro,7α-bromo-6-nitrocholest-5-ene (LXXXIX)

M^+ 527 (31.00)/529 (18.00)/531 (18.00) ($C_{27}H_{43}NO_2BrCl$), m/z 485 (10.00), 483 (30.00), 481 (30.00), 450 (5.00), 449 (27.50), 448 (100), 447 (88.00), 436 (10.00), 434 (10.00), 433 (10.00), 432 (27.00), 431 (12.00), 430 (27.00), 419 (6.50), 418 (14.20), 414 (7.00), 413 (14.50), 412 (44.00), 404 (15.00), 403 (37.50), 402 (32.00), 401 (7.00), 400 (7.50), 396 (7.50), 395 (10.00), 394 (22.50), 392 (12.80), 378 (7.50), 376 (7.50), 366 (12.50), 365 (13.50), 364 (15.00), 350 (7.00), 338 (12.50), 337 (9.00), 334 (10.00), 324 (14.50), 322 (32.50), 318 (7.50), 308 (7.50), 296 (7.50), 294 (12.50), 282 (17.50), 280 (16.00), 278 (6.00), 268 (15.00), 263 (7.50), 261 (6.00), 247 (12.50), 239 (5.00), 234 (5.00), 226 (5.00), 214 (12.50), 205 (11.00), 195 (11.00), 194 (7.50), 181 (16.00), 172 (6.80), 167 (12.50), 157 (9.00), 140 (11.00), 138 (9.00), 137 (7.50), 135 (9.50), 133 (7.50), 127 (49.00), 126 (20.00), 124 (19.00), 122 (9.00), 114 (29.00), 112 (30.00), 110 (20.00), 108 (10.00), 100 (7.50), 98 (33.00), 96 (27.00), 94 (10.00), 86 (17.50), 83 (42.50), 82 (15.00), 81 (18.00), 79 (12.50), 69 (26.90), 57 (60.00), 55 (5.00), 43 (9.00), 36 (9.00).

4β,7α-Dibromo-6-nitrocholest-5-ene (XC)

M^+ 571/573/575 (Absent; $C_{27}H_{43}NO_2Br_2$), m/z 494 (17.00), 492 (17.00), 413 (21.00), 412 (27.00), 398 (12.50), 396 (27.00), 394 (15.00), 384 (10.00), 380 (7.60), 372 (5.00), 370 (11.00), 300 (15.00), 247 (12.50), 190 (10.00), 189 (28.50), 188 (7.50), 161 (16.10), 140 (16.50), 131 (27.50), 125 (13.00), 123 (13.00), 121 (17.50), 119 (16.00), 115 (55.00), 114 (24.00), 109 (24.00), 95 (45.00), 93 (25.00), 91 (31.50), 83 (35.00), 82 (42.50), 81 (50.00), 80 (40.00), 79 (21.50), 77 (9.85), 71 (40.00), 69 (50.00), 67 (26.00), 58 (30.00), 57 (62.50), 55 (51.00), 42 (80.00), 40 (100).

3α,4α-Epoxy-6-nitrocholest-5-ene (CIII)

M^+ 429 (1.00, $C_{27}H_{43}NO_3$), m/z 414 (6.00), 413 (8.00), 412 (14.00), 400 (9.00), 396 (12.00), 395 (27.00), 393 (12.00), 386 (20.00), 384 (19.00), 383 (26.00), 382 (19.00), 373 (48.00), 372 (100), 370 (18.00), 369 (14.00), 368 (22.00), 366 (12.00), 365 (12.00), 356 (30.00), 354 (19.00), 353 (21.50), 344 (12.00), 330 (6.00), 329 (13.00), 328 (10.00), 316 (5.00), 302 (10.00), 299 (4.00), 298 (7.00), 286 (6.00), 284 (8.00), 274 (9.50), 270 (10.00), 260 (23.00), 258 (18.00), 175 (10.00), 174 (18.00), 173 (10.00), 161 (12.00), 159 (15.20), 157 (11.50), 149 (20.00),

147 (17.50), 145 (17.00), 135 (35.00), 133 (22.00), 131 (16.50), 129 (14.00), 123 (13.00), 121 (28.00), 119 (24.00), 117 (16.00), 109 (38.50), 107 (42.00), 105 (32.00), 97 (30.00), 95 (62.00), 93 (42.00), 91 (37.00), 83 (46.00), 81 (70.00), 79 (40.00), 71 (53.00), 69 (72.00), 67 (42.00), 57 (98.00), 55 (95.00),

6-Nitrocholest-5-eno [4β,3α-d]-2-vinyl-2-oxazoline (CV)

$M^{+\cdot}$ 482 (18; $C_{30}H_{46}N_2O_3$), m/z 466 (4.00), 465 (12.00), 451 (9.00), 450 (22.00), 438 (14.00), 437 (66.00), 436 (100), 435 (32.00), 419 (8.00), 417 (10.00), 370 (8.00), 366 (7.00), 354 (6.00), 344 (4.00), 308 (3.00), 372 (8.00), 269 (16.00), 260 (8.00), 259 (18.00), 241 (4.00), 165 (11.00), 150 (8.00), 149 (43.0), 147 (19.00), 133 (9.00), 129 (51.50), 119 (10.00), 113 (16.00), 112 (28.00), 111 (18.00), 109 (16.50), 107 (13.00), 105 (11.80), 99 (10.00), 97 (24.00), 95 (27.00), 93 (14.00), 91 (11.00), 85 (22.00), 83 (38.00), 81 (28.00), 79 (15.00), 73 (12.20), 71 (62.80), 69 (46.00), 59 (24.00), 57 (100), 55 (84.00), 44 (52.00), 43 (81.00), 40 (80.00).

3α-Hydroxy-6β-acrylamido-6-nitrocholest-5-ene (CVI)

$M^{+\cdot}$ 500 (2.00; $C_{30}H_{48}N_2O_4$), m/z 483 (10.00), 482 (18.00), 465 (12.00), 455 (34.50), 454 (100), 453 (32.00), 437 (28.50), 436 (77.00), 435 (34.00), 426 (12.00), 425 (32.00), 419 (8.00), 410 (6.00), 401 (12.00), 399 (25.00), 398 (68.00), 386 (18.00), 384 (15.00), 373 (24.00), 372 (63.00), 371 (10.00), 366 (9.00), 345 (6.00), 344 (9.00), 330 (23.00), 329 (22.00), 318 (6.50), 317 (20.00), 302 (3.80), 298 (3.00), 247 (8.50), 188 (15.00), 175 (20.00), 173 (17.00), 161 (20.00), 159 (20.00), 150 (24.00), 149 (28.00), 147 (26.00), 145 (26.00), 143 (14.00), 123 (24.00), 121 (35.00), 119 (30.00), 111 (18.00), 109 (46.00), 107 (54.00), 105 (43.00), 100 (12.00), 97 (40.00), 95 (88.00), 93 (60.00), 91 (44.00), 85 (14.00), 83 (57.00), 81 (100), 79 (54.00), 77 (21.50), 72 (100), 69 (98.00), 57 (100), 56 (100), 43 (100), 41 (100).

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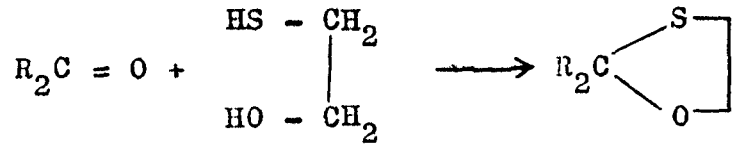
PART TWO

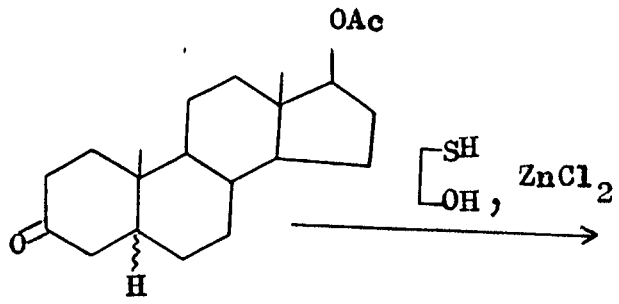
Synthesis of Steroidal Oxathiolanes

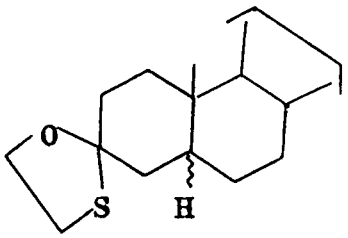
Theoretical

A number of steroidal as well as non steroidal ketones have been reported to condense readily with β -mercaptoethanol to furnish Oxathiolanes. The methods for effecting the condensation of ketones with ethanedithiol or β -mercapto-ethanol include use of zinc chloride and sodium sulphate[1], hydrogen chloride in ether,[2] p-toluenesulphonic acid in benzene under azeotropic distillation employing water separator and an exchange method.[3,4]



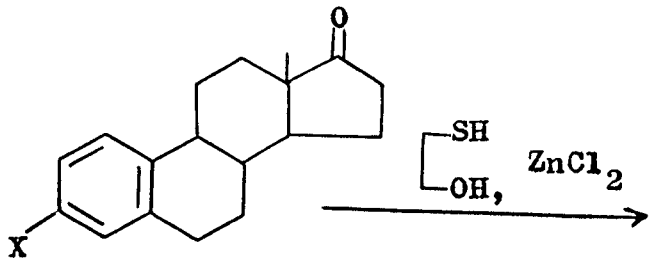
Romo and coworkers[1] showed that β -mercaptoethanol reacts readily in the presence of zinc chloride with unconjugated carbonyl group to yield the corresponding hemithioketals. Thus androstan-17β-ol-3-one-17-acetate (I), etiocholan-17β-ol-3-one-17-acetate (III) estrone and its acetate (V and VI), Δ^5-androstan-3β-ol-17-one-3-acetate (IX), allopregnan-3β-ol-20-one and its 3β-acetate (XI and XII) as well as Δ^5-pregnan-3-ol-20-one and its 3β-acetate (XV and XVI) were converted into corresponding oxathiolanes (II, IV, VII, VIII, X, XIII, XIV, XVII and XVIII).

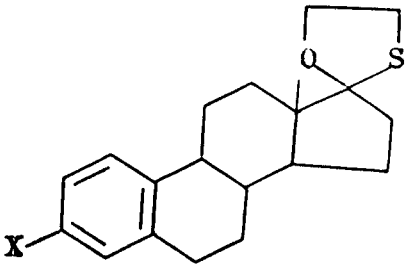




(I) 5α-H
(III) 5β-H

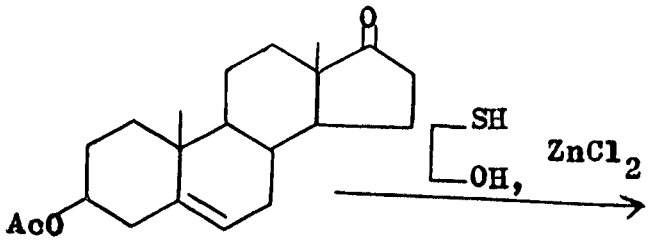
(II) 5α-H
(IV) 5β-H

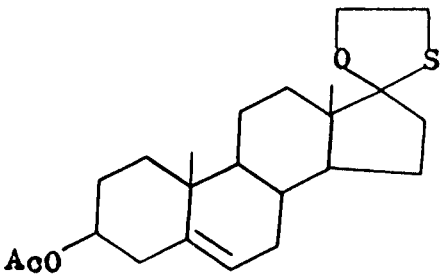




(V) X = OH
(VI) X = OAc

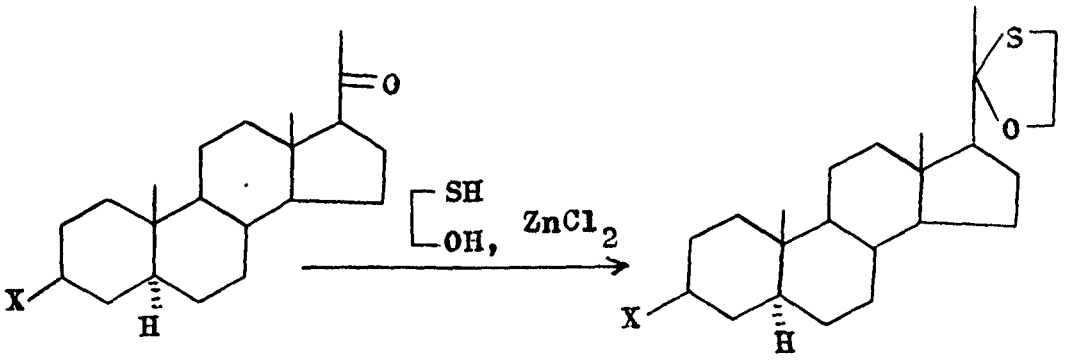
(VII) X = OH
(VIII) X = OAc





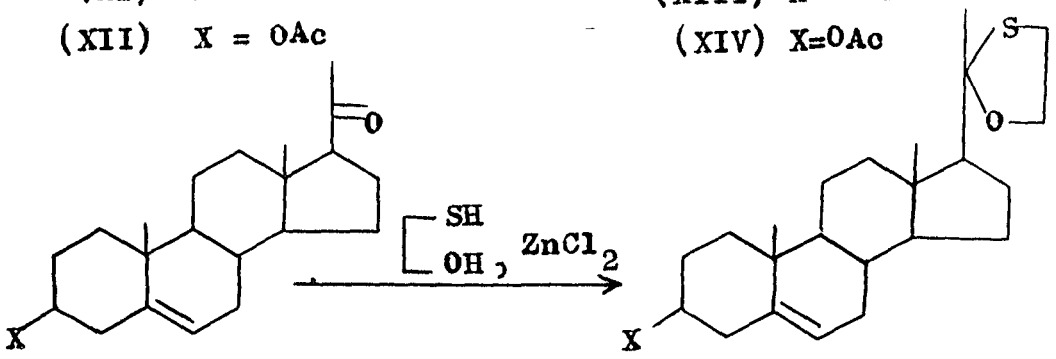
(IX)

(X)



(XI) X = OH
(XII) X = OAc

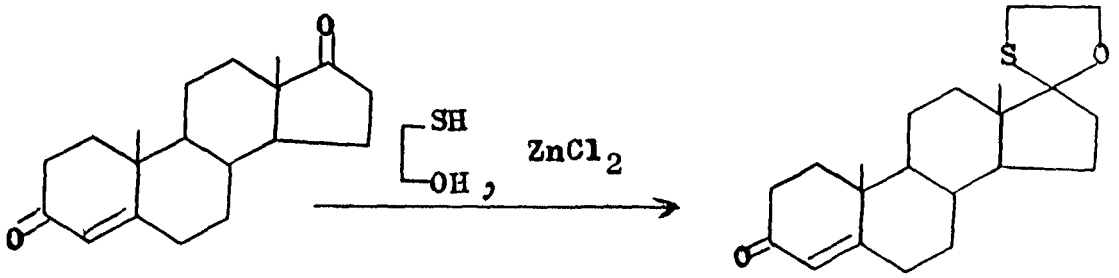
(XIII) X = OH
(XIV) X=OAc



(XV) X = OH
(XVI) X = OAc

(XVII) X = OH
(XVIII) X = OAc

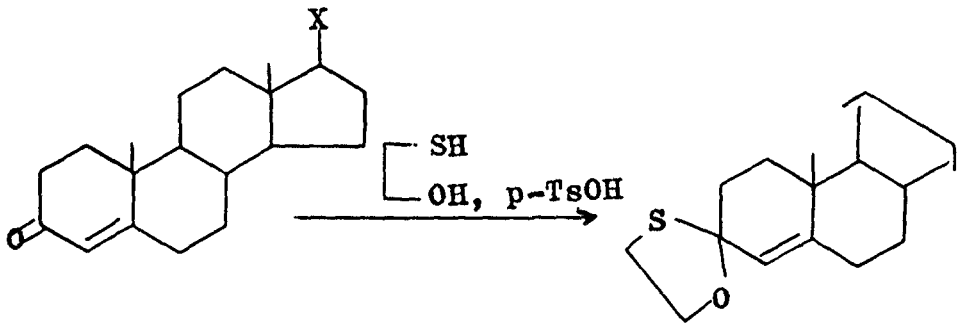
Romo and coworkers[1] also showed that α,β-unsaturated ketones do not react with β-mercaptoethanol in the presence of zinc chloride but a saturated carbonyl reacts selectively, Δ^4-androsten-3,17-dione afforded corresponding 17-ethylene hemithioketal (XX).



(XIX)

(XX)

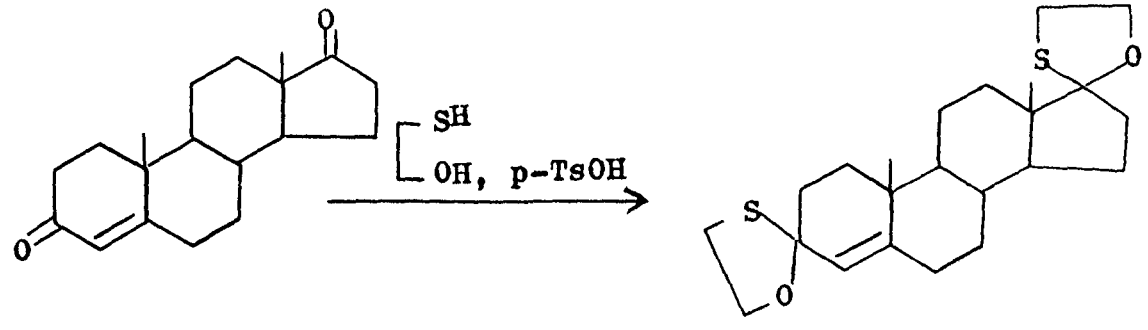
α,β-Unsaturated ketones react with β-mercaptoethanol in the presence of p-toluenesulphonic acid. Thus testosterone and its acetate (XXI and XXII) were converted to the 3-ethylene hemithioketals (XXIII and XXIV) in less than 20% yield.[1]



(XXI) X = OH
(XXII) X = OAc

(XXIII) X = OH
(XXIV) X = OAc

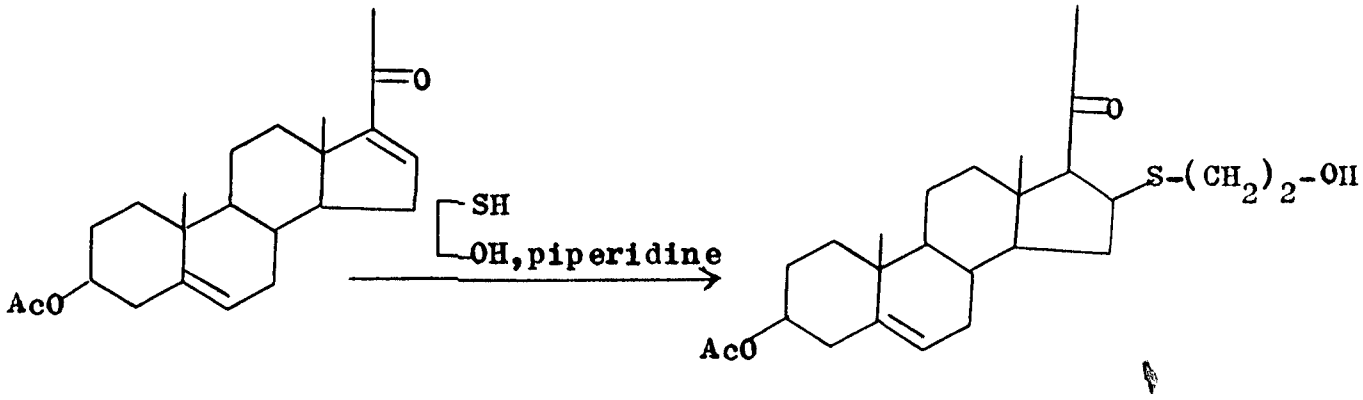
Androst-4-en-3,17-dione (XIX) under similar reaction conditions provided 3,17-bisethylene hemithioketal (XXV).



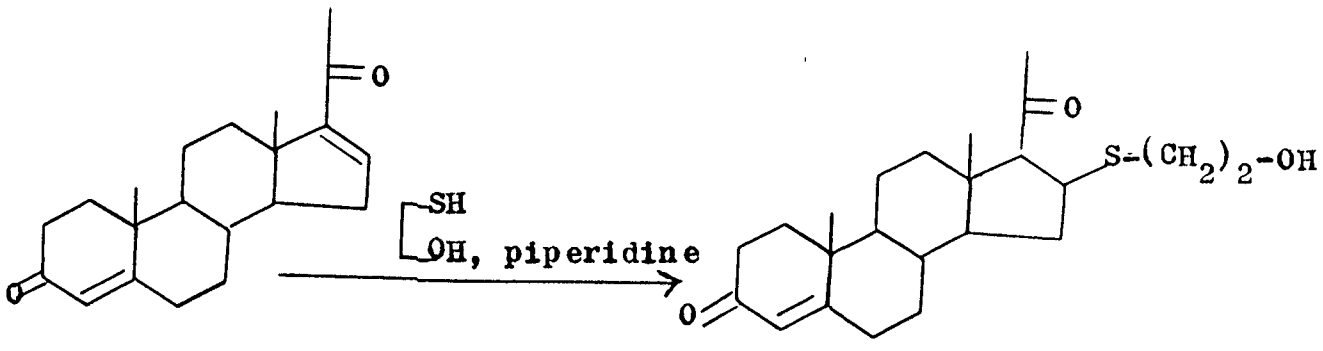
(XIX)

(XXV)

β -Mercaptoethanol undergoes 1,4-addition with sterically unhindered α,β -unsaturated ketones in the presence of piperidine. Thus $\Delta^{5,16}$-pregnnadin-3β-ol-20-one-3-acetate (XXVI) and $\Delta^{4,16}$-pregnnadin-3,20-dione (XXVII) afforded corresponding 16β-hydroxyethylmercapto derivatives (XXVIII) and (XXIX) in excellent yields.[2]

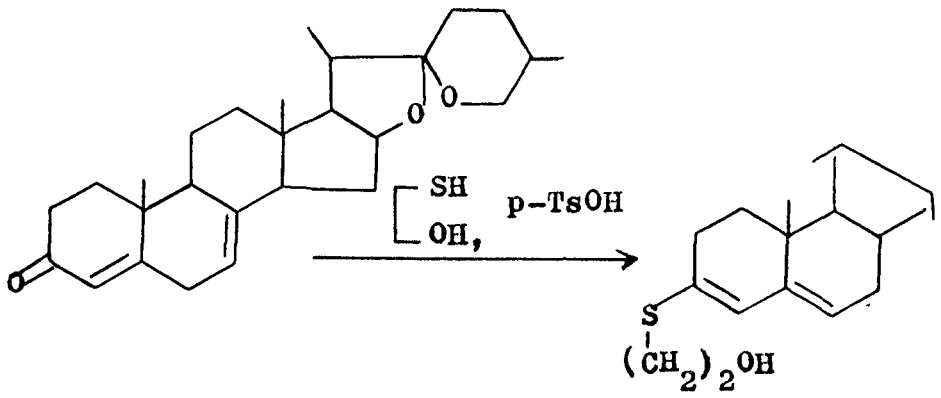


(XXVI) (XXVIII)



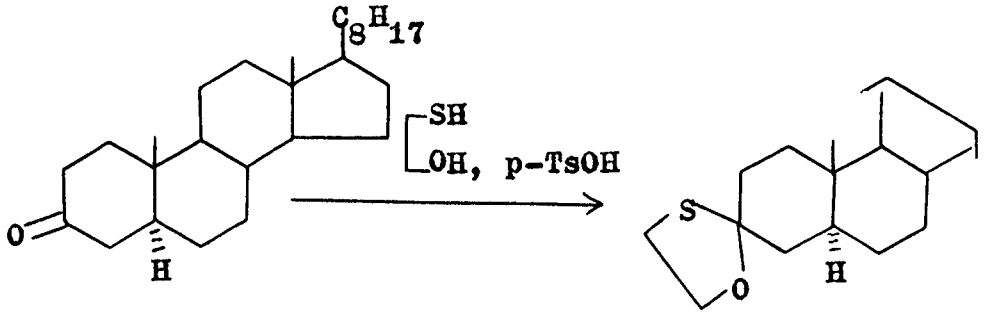
(XXVII) (XXIX)

Djerassi and Gormann[3] reported that $\Delta^{4,7}$-22n-spirodien-3-one (XXX) with β-mercaptoethanol in the presence of p-toluenesulphonic acid furnished (XXXI) in about 20% yield.

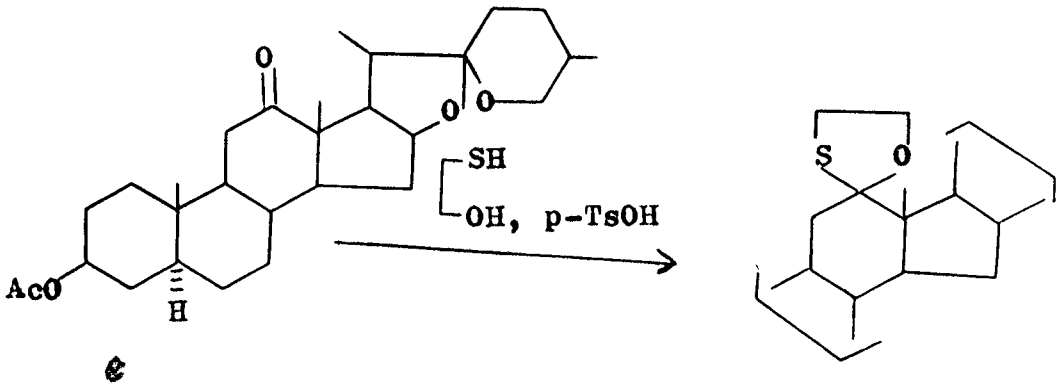


(XXX) (XXXI)

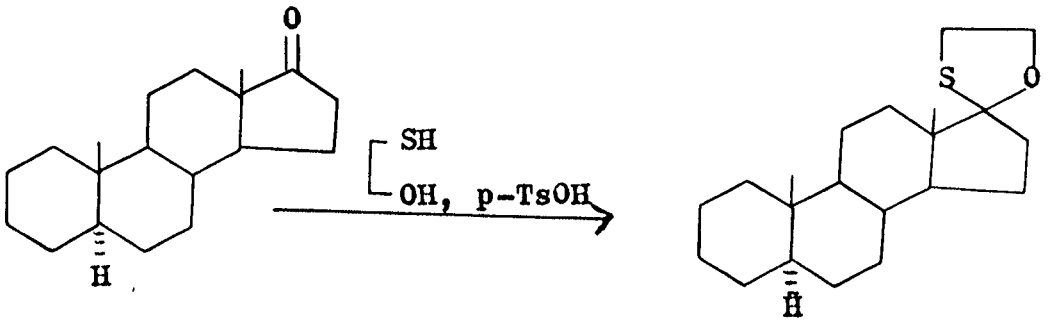
Djerassi and Gormann[3] also obtained a number of hemithioketals by refluxing the ketones with β-mercapto-ethanol in dry benzene using p-toluenesulphonic acid as a catalyst. This method is found satisfactory for the formation of ethylene hemithioketal of saturated ketones (XXXII, XXXIV, XXXVI and IX) but unsaturated ketones like Δ^4-3-ketosteroids (XXI, XXXVIII and XL) gave the desired product in poor yield.



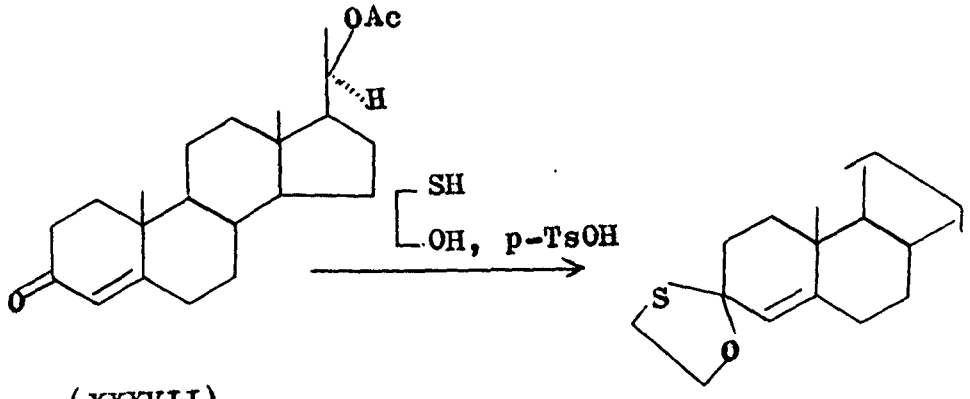
(XXXII) (XXXIII)



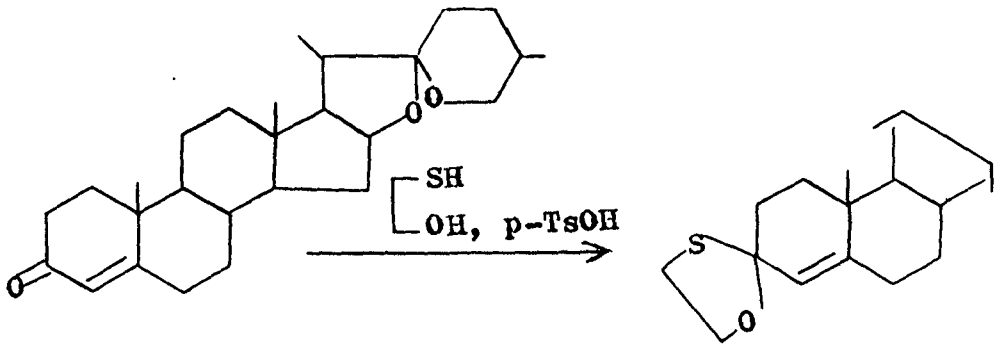
(XXXIV) (XXXV)



(XXXVI) (XXXVII)

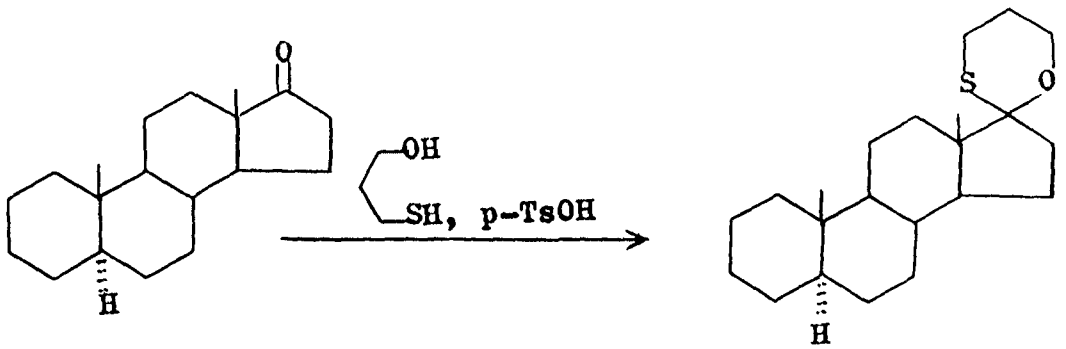


(XXXVII) (XXXIX)

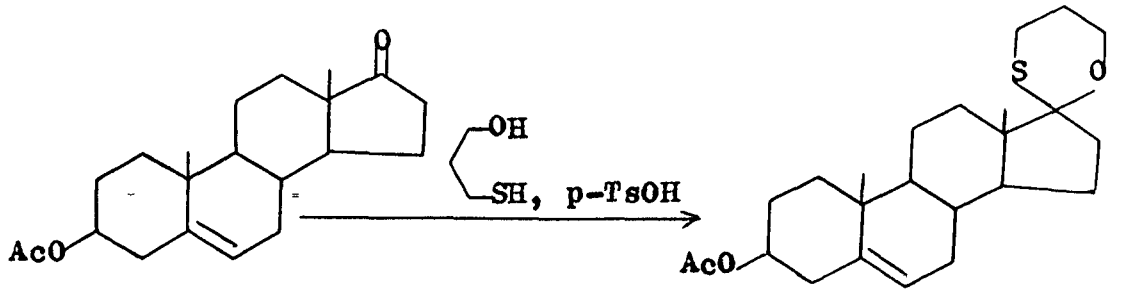


(XL) (XLI)

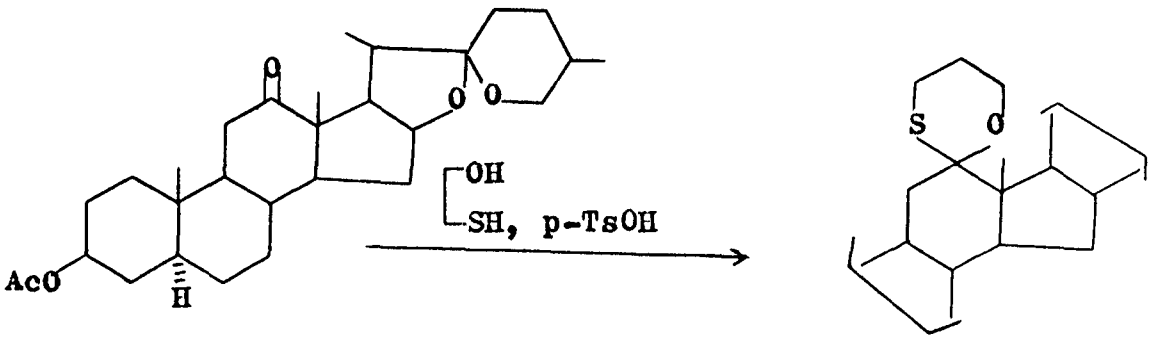
ω-Mercaptopropanol in the presence of p-toluenesulphonic acid undergoes condensation with a number of ketones (XXXVI, IX, XXXIV, XLV) forming trimethylene hemithioketals (XLII, XLIII, XLIV and XLVI)[1].



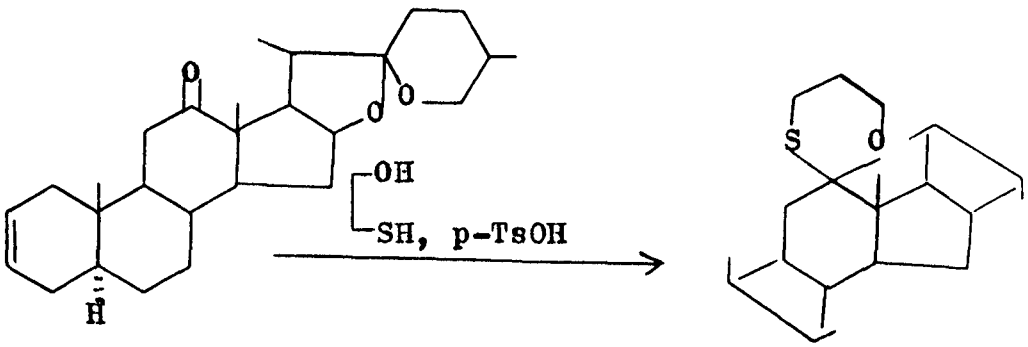
(XXXVI) (XLII)



(IX) (XLIII)

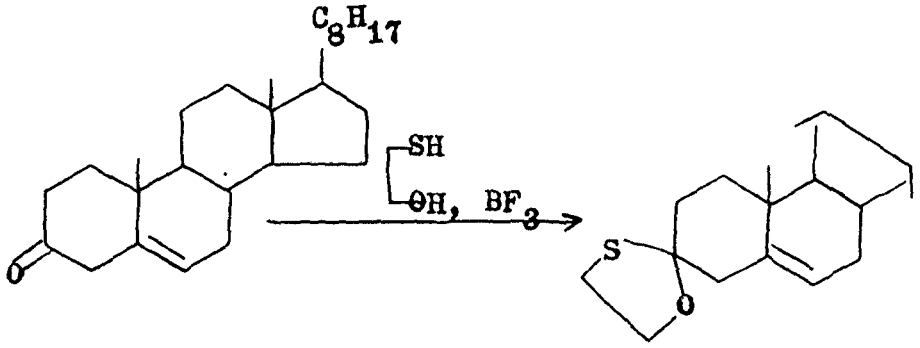


(XXXIV) (XLIV)



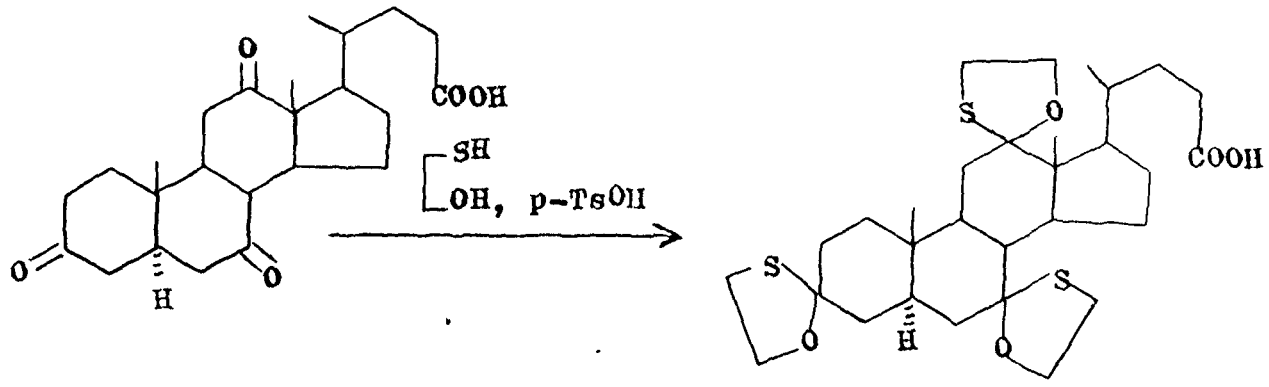
(XLV) (XLVI)

Fieser[5] converted ketones (XXXII and XLVII) into corresponding hemithioketals (XXXIII) and (XLVIII) using β-mercaptoethanol and BF_3-etherate as condensing agent.



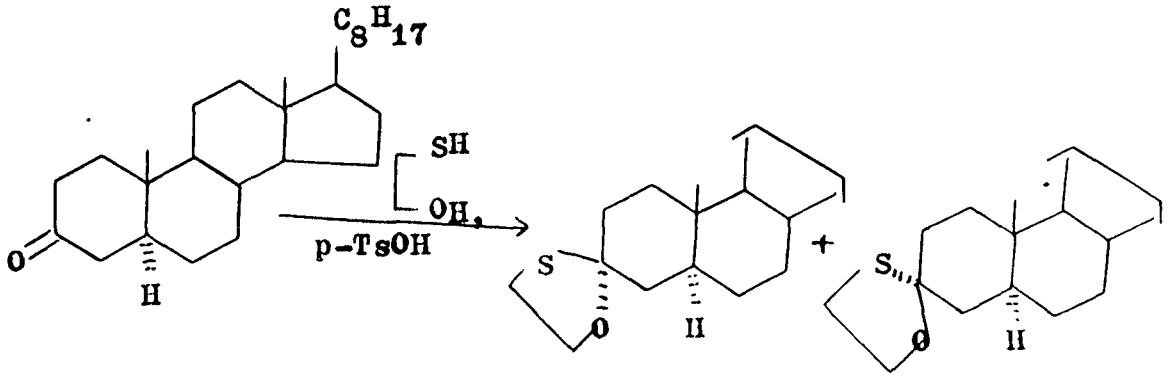
(XLVII) (XLVIII)

Robert and Brown[6] reported that the treatment of dehydrocholic acid (XLIX) with β-mercaptoethanol in the presence of p-toluenesulphonic acid gave the dehydrocholic acid trimethyloethylene ketal (L).



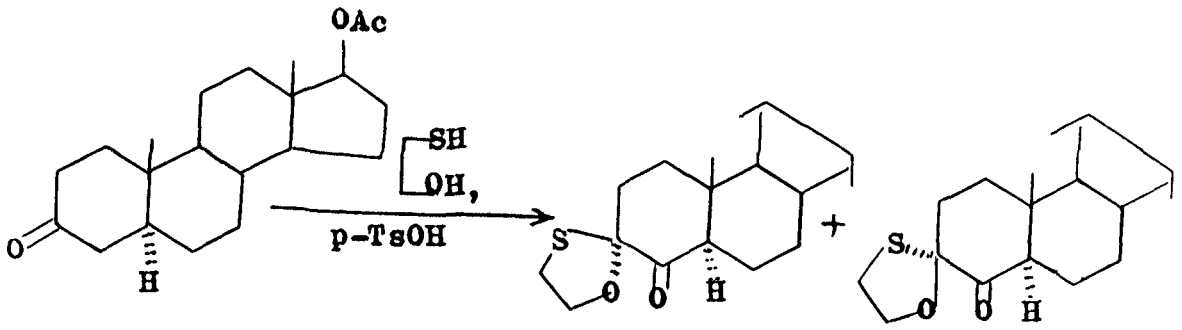
(XLIX) (L)

Eliel et al.[7] observed that when 5α-cholestan-3-one (XXXII) was treated with β-mercaptoethanol in dry benzene using p-toluenesulphonic acid as catalyst, two pure diastereoisomeric oxathiolanes (LI and LII) were obtained while the previous result[3] showed the formation of a single product.



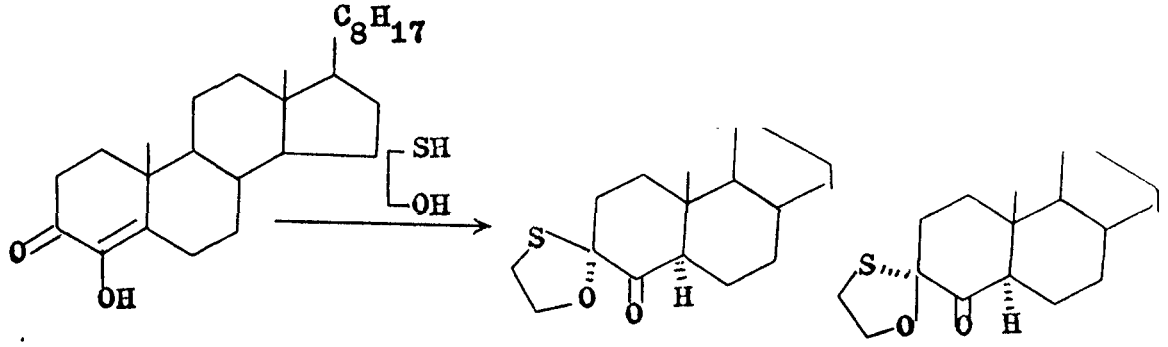
(XXXII) (LI) (LII)

Karmas[8] obtained two diastereoisomeric hemithioketals (LIII and LIV) from 5α-dihydrotestosterone acetate (I) using β-mercaptoethanol and p-toluenesulphonic acid.



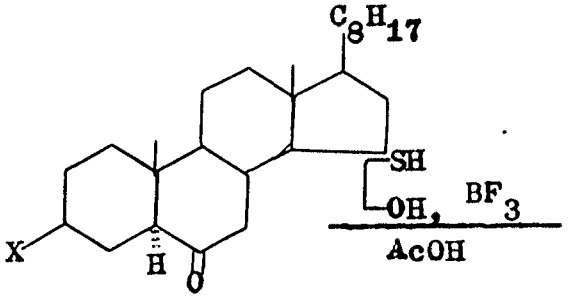
(I) (LIII) (LIV)

Cooper et al.[9] reported that the treatment of 4-hydroxy cholest-4-en-3-one (LV) with β-mercaptoethanol provided two isomeric hemithioketals (LVI and LVII).

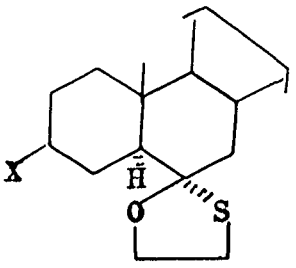


(LV) (LVI) (LVII)

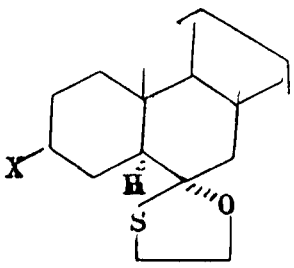
The treatment of 5α-cholestan-6-one (LVIII) and its 3β-chloro (LIX), 3β-acetoxy (LX) and 3β-hydroxy (LXI) analogues with β-mercaptoethanol in the presence of boron trifluoride gave the corresponding 6β-oxy-6α-thiodimethylene (LXII - LXV) together with 6α-oxy-6β-thiodimethylene (LXVI - LXIX).[10]



	X
(LVIII)	H
(LIX)	Cl
(LX)	OAc
(LXI)	OH

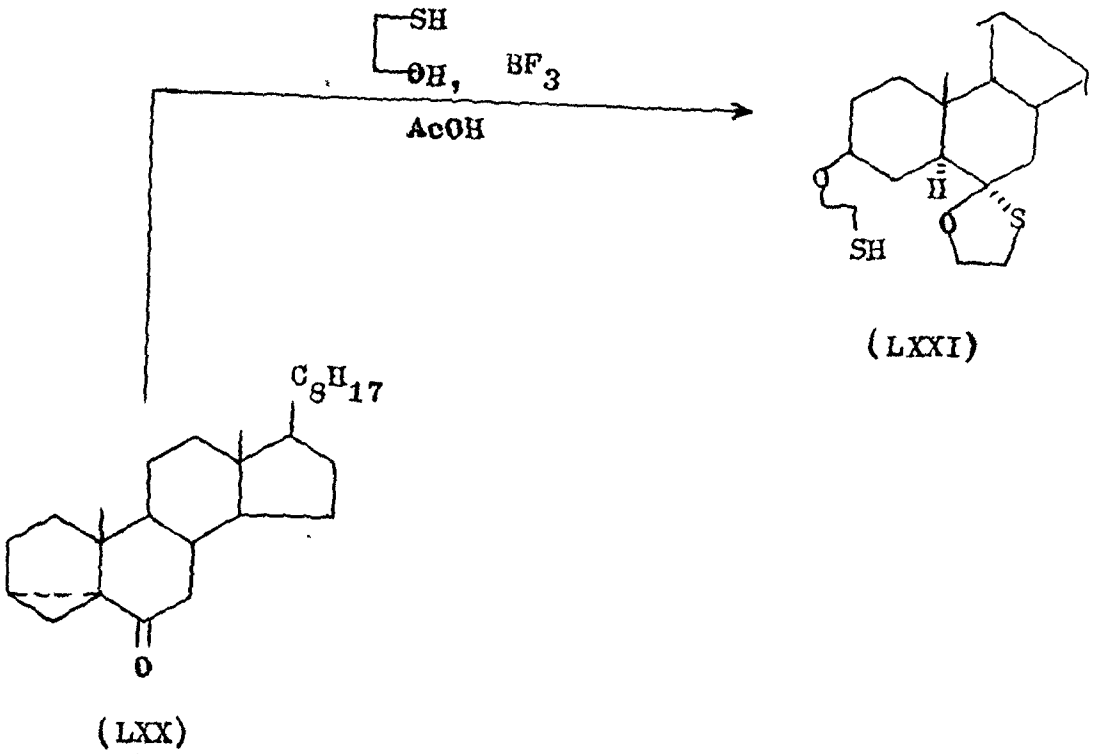


	X
(LXII)	H
(LXIII)	Cl
(LXIV)	OAc
LXV)	OH



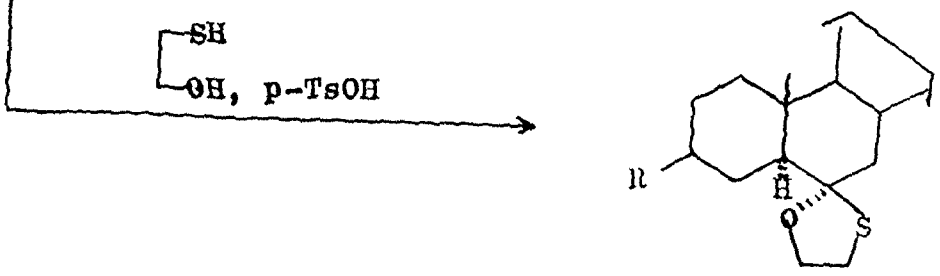
	X
(LXVI)	H
(LXVII)	Cl
(LXVIII)	OAc
(LXIX)	OH

It was also found that the treatment of 3α,5-cyclo-5α-cholestan-6-one (LXX) with β-mercaptoethanol in the presence of p-toluenesulp honic acid gave hemithioketals (LXXII-LXXIV). Similar treatment of (LXX) in the presence of BF_3-etherate provided the hemithioketals (LXXI).[11]



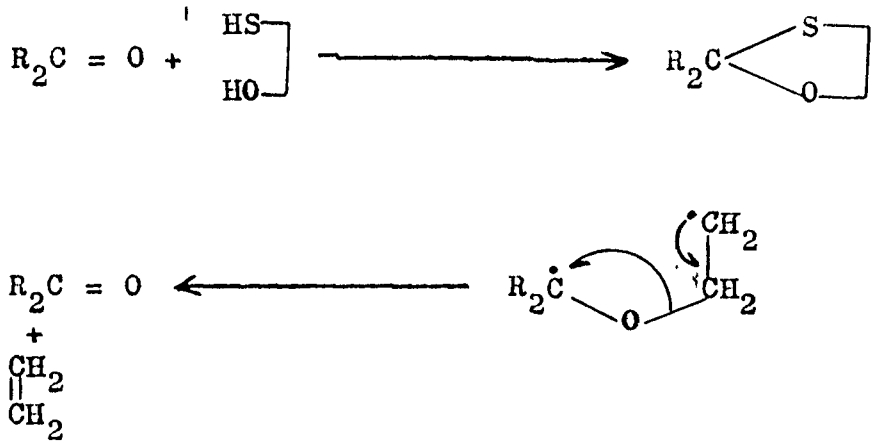
(LXXI)

(LXX)



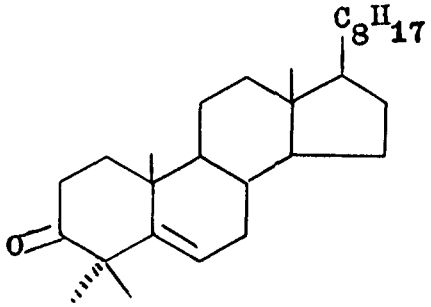
	R
(LXXII)	OTs
(LXXIII)	$-SCH_2CH_2OH$
(LXXIV)	$-SCH_2CH_2OAc$

Oxathiolanes on acid hydrolysis or on treatment with Raney nickel are converted to parent ketones.[1] The mechanism of the desulfurization of hemithioketal by Raney nickel to produce parent ketone, was first given by Djerassi et al.[3] It was suggested that the reaction may proceed via a 1,4-diradical as shown below.

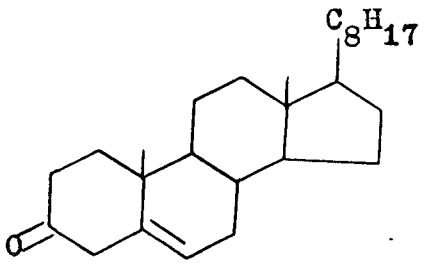


Discussion

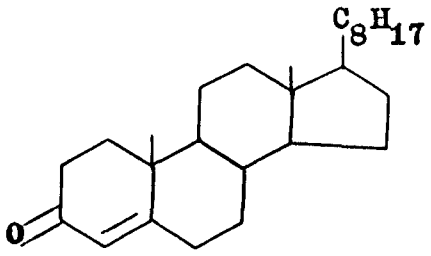
Several papers dealing with the synthesis and structure of steroidal oxathiolanes have appeared.[1,3,10,11,15] The present work is concerned with the synthesis of isomeric oxathiolanes from 4,4-dimethylcholest-5-en-3-one (LXXV), cholest-5-en-3-one (XLVII) and cholest-4-en-3-one (LXXVI).



(LXXV)



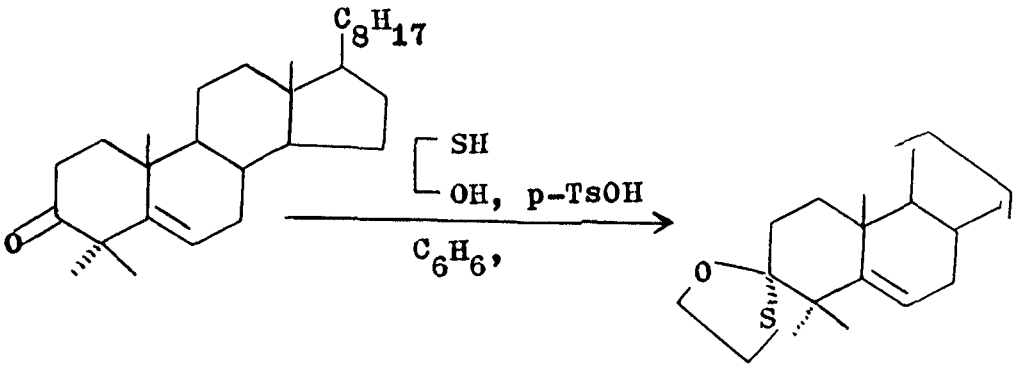
(XLVII)



(LXXVI)

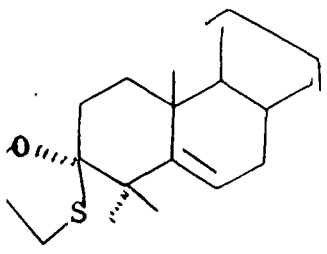
Reaction of 4,4-dimethyl cholest-5-en-3-one (LXXV) with β -mercaptoethanol

4,4-Dimethyl cholest-5-en-3-one (LXXV) was treated with β -mercaptoethanol in dry benzene using p-toluenesulphonic acid as a catalyst. After the completion of reaction, the reaction mixture was worked up in the usual manner and chromatographed over silica gel to provide two compounds, m.p. 130° and m.p. 140°.



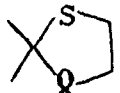
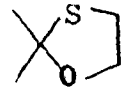
(LXXV)

(LXXVII)



(LXXVIII)

Characterization of the compounds, m.p. 130° as 3β-oxy, 3α-thiodimethylene, 4,4-dimethyl cholest-5-ene (LXXVII) and the compound, m.p. 140° as 3α-oxy,3β-thiodimethylene, 4,4-dimethyl cholest-5-ene (LXXVIII)

The mass spectra of (LXXVII) and (LXXVIII) gave the molecular ion peaks at m/z 472 and both were analysed for $C_{31}H_{52}OS$ (positive sodium nitroprusside test for sulphur). The molecular composition shows that they were isomeric. The IR spectrum of compound (LXXVII) m.p. 130° exhibited bands at 1220 cm^{-1} (strong) which shows the presence of $-CH_2$ group next to unoxidized sulphur atom[12,13], 1150, 1088 cm^{-1} (C-O) linkage of the hemithioketal ring.[14] The pronounced band observed at 1045 cm^{-1} is characteristic for the hemithioketal  grouping.[14] The IR spectrum of the compound, m.p. 140° gave bands at 1220, 1230 cm^{-1} strong ($-S-CH_2$), 1149, 1090 (C-O linkage of the hemithioketal ring), and a sharp peak at 1060 cm^{-1}  . Thus the I.R. data and elemental analyses revealed that the reaction has taken place in the usual manner and hemithioketal rings were present in both the compounds but the difference lies in the orientation of $C_{Spirane}O$ and $C_{Spirane}S$ bonding. Since sulphur atom of the β-mercaptoethanol has almost the equal probability of attacking the carbonyl group from both the sides (front and back), therefore two isomeric compounds with C-S bonds as axial and equatorial are plausible. The distinction between

(LXXVII) and (LXXVIII) may be made with the help of their N.M.R. spectra.[10,15] The N.M.R. spectrum of (LXXVII) revealed a distorted triplet for two protons at δ 4.2 for ($OC\underline{H}_2$), a clear triplet integrating for two protons at δ 2.9 for ($S-C\underline{H}_2$) and a multiplet at δ 5.5 for C6-$\underline{H}$. The N.M.R. spectrum of (LXXVIII) exhibited two distorted triplets at δ 4.3 and 4.0 each integrating for one proton each for $OC\underline{H}_2$. A double doublet integrating for two protons at δ 2.83 was assigned to $SC\underline{H}_2$. A multiplet for vinylic proton (C6-$\underline{H}$) was also observed at δ 5.5.

The most striking difference in N.M.R. spectra of compounds (LXXVII) and (LXXVIII) was the splitting pattern of $-OCH_2$ and $-SCH_2$ protons. The appearance of two distorted triplets and a double doublet in N.M.R. spectrum of (LXXVIII) may be explained by assuming that the methylene protons bonded with the axially oriented oxygen atom are magnetically non equivalent. Thus they behave differently towards the applied field and appeared at different chemical shifts, in the N.M.R. spectrum while methylene protons attached to the sulphur atom are almost magnetically equivalent. Two distorted triplets at δ 4.3 and 4.0 were due to pseudoequatorial and pseudoaxial protons ($OC\underline{H}_2$, non equivalent) resulting by the splitting with SCH_2 (magnetically equivalent)

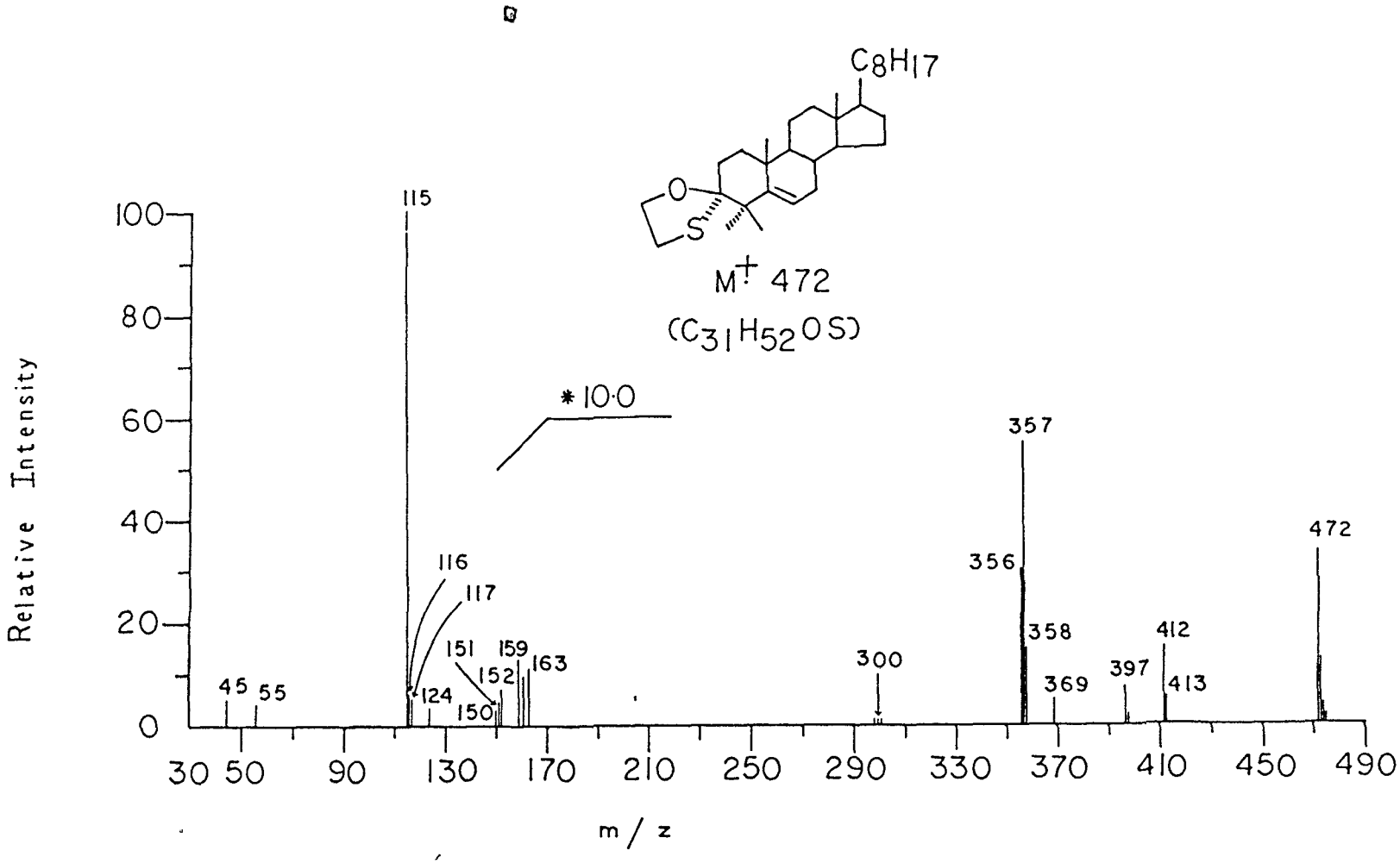


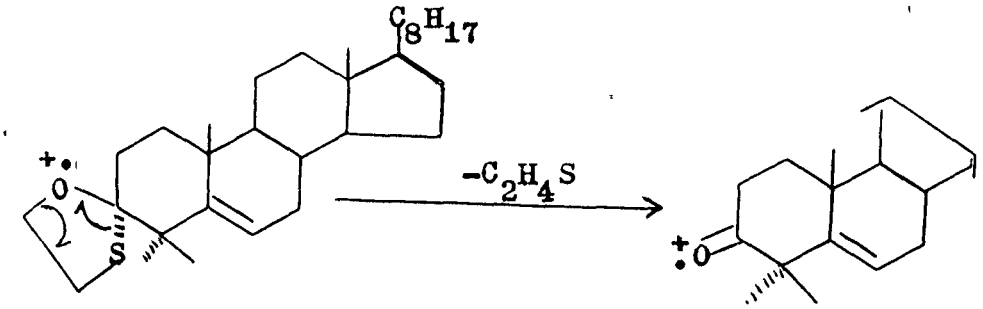
Fig.1 Mass Spectrum of LXXVII.

protons. A double doublet for SCH_2 results by the splitting with pseudo equatorial and pseudoaxial protons ($-OCH_2$). The distortion in triplets may be considered due to the long range coupling. Methyl signals were seen at δ 1.1 (C10-CH_3), 0.66 (C13-CH_3), 1.20, 0.90, 0.80 (other methyl protons).

In case of (LXXVII) where $O-CH_2$ bond was equatorially oriented, the methylene protons were almost magnetically equivalent and same for the methylene protons of $S-CH_2$ group. The triplets at δ 4.2 and 2.9 each integrating for two protons ($-OCH_2$ and $-S-CH_2$) were due to the splitting of each other. The distortion in triplet of $O-CH_2$ protons at δ 4.2 might be considered due to the long range couplings. Methyl signals were observed at δ 1.1 (C10-CH_3), 0.66 (C13-CH_3), 1.25, 0.90, 0.80 (other methyl protons). The compounds (LXXVII) and (LXXVIII) on treatment with aqueous acetic acid regenerated the parent ketone (LXXV).

The structures (LXXVII) and (LXXVIII) were further supported by their mass spectral studies. The mass spectrum of (LXXVII) (Fig. 1) gave molecular ion peak at m/z 472. Other peaks of significance were recorded at m/z 412 ($M-C_2H_4S$), m/z 397 (m/z 412-CH_3), m/z 398, m/z 369 (m/z 412-CO & CH_3), m/z 358, m/z 357, m/z 356, m/z 299 (m/z 412-C_8H_{17}), m/z 115 (base peak; C_5H_7OS) and m/z 55 (C_3H_3O). The peak M-60 corresponding to loss of C_2H_4S was conspicuous in the mass spectrum of (LXXVII) at m/z 412. The loss of mass 60 from hemithioketal is well known.[16]

m/z 412 ($M-C_2H_4S$)

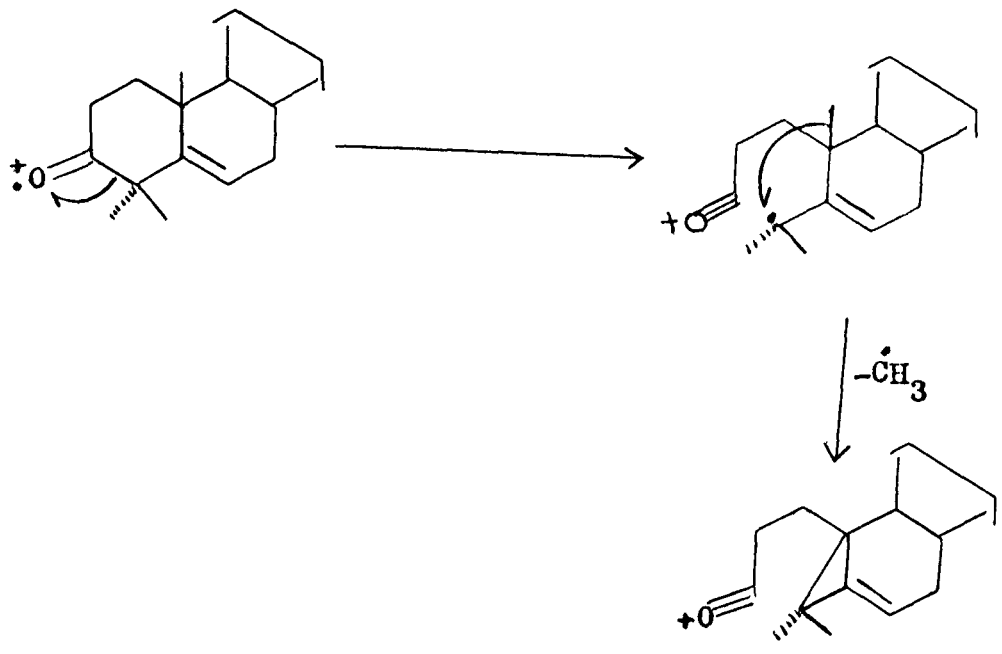


(LXXVII)
$M^+_{\bullet}$ 472
($C_{31}H_{52}OS$)

m/z 412
($C_{29}H_{48}O$)

m/z 397 (m/z 412-CH_3)

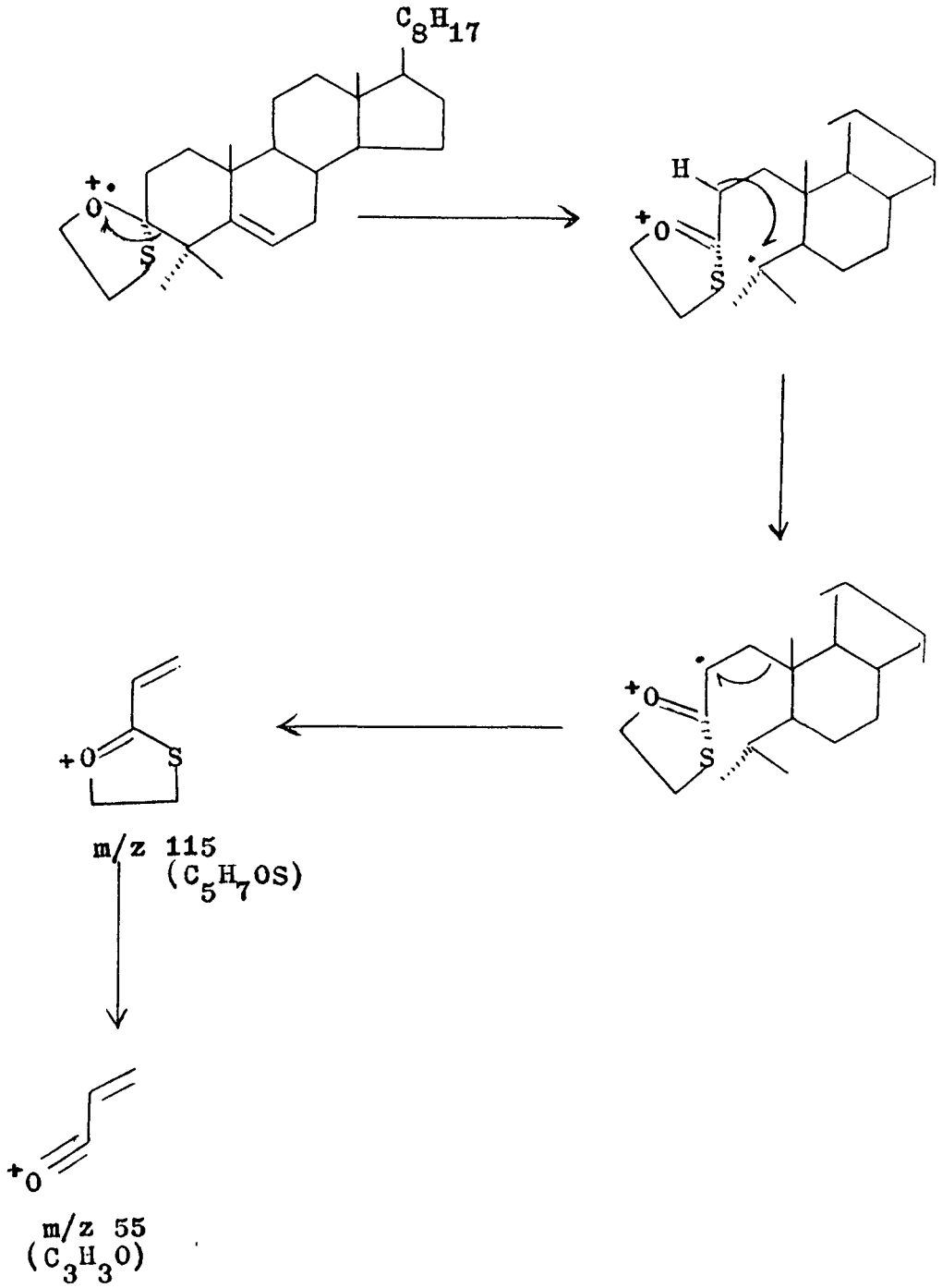
The loss of methyl group from the fragment ion m/z 412 gave rise to ion m/z 397.



m/z 397

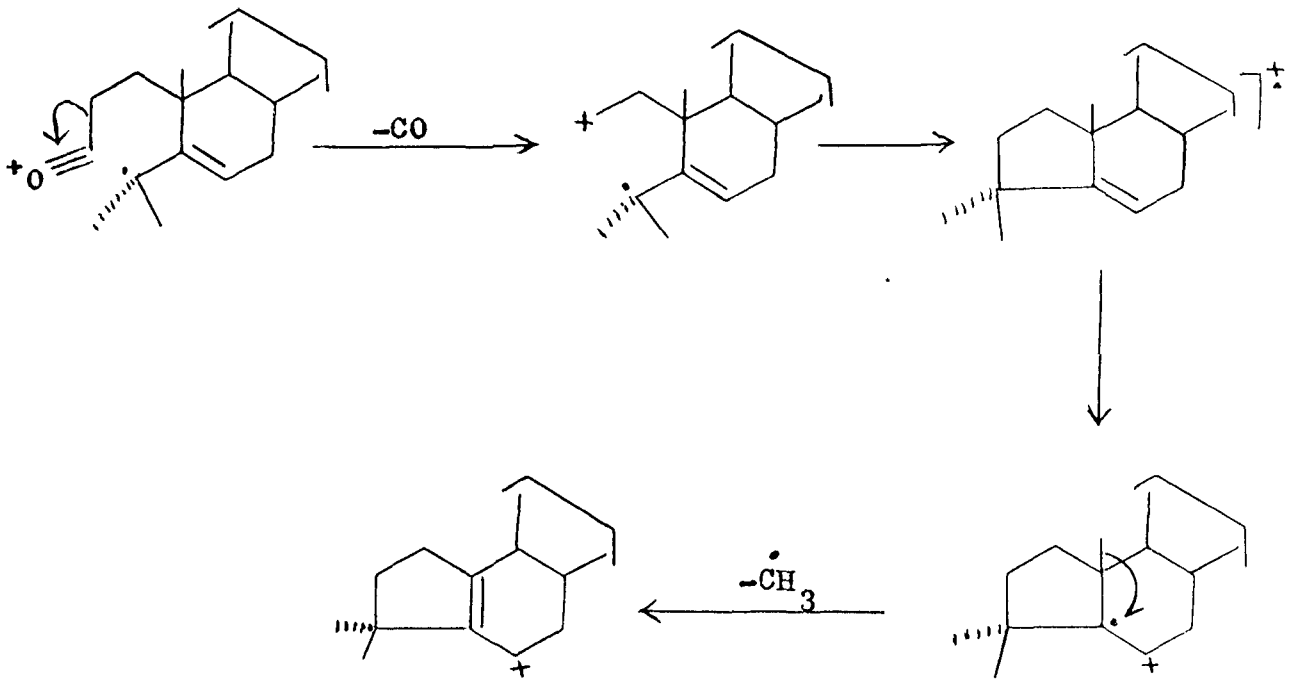
m/z 115 and 55

The formation of fragment ions m/z 115 and 55 may be rationalized as follows.



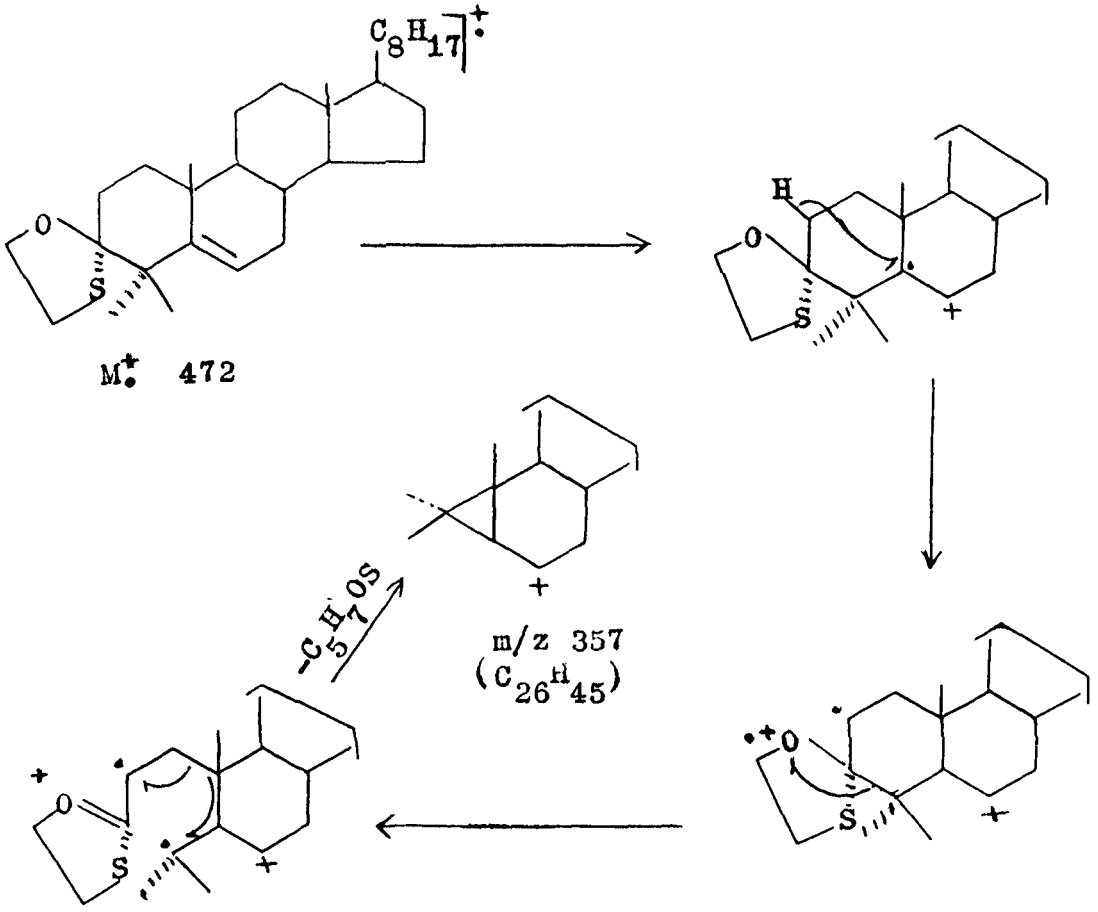
m/z 369

This ion may be shown to arise by the loss of CO and CH_3 groups from the fragment ion m/z 412.



m/z 369
($C_{27}H_{45}$)

The formation of ion at m/z 357 can be rationalized from molecular ion as follows.



The mass spectrum of (LXXVIII) (Fig. 2) showed molecular ion peak at m/z 472 and base peak at m/z 43. Other peaks of significance from (LXXVIII) were recorded at m/z 412 ($M^{+\bullet}-C_2H_4S$), m/z 397 (m/z 412-CH_3), m/z 395, m/z 369 (m/z 412-CO-& CH_3), m/z 358, m/z 357, m/z 356, m/z 299, m/z 115, m/z 55 and lower mass peaks. The formation of some of the significant fragment ions can be rationalized in Scheme - 1.

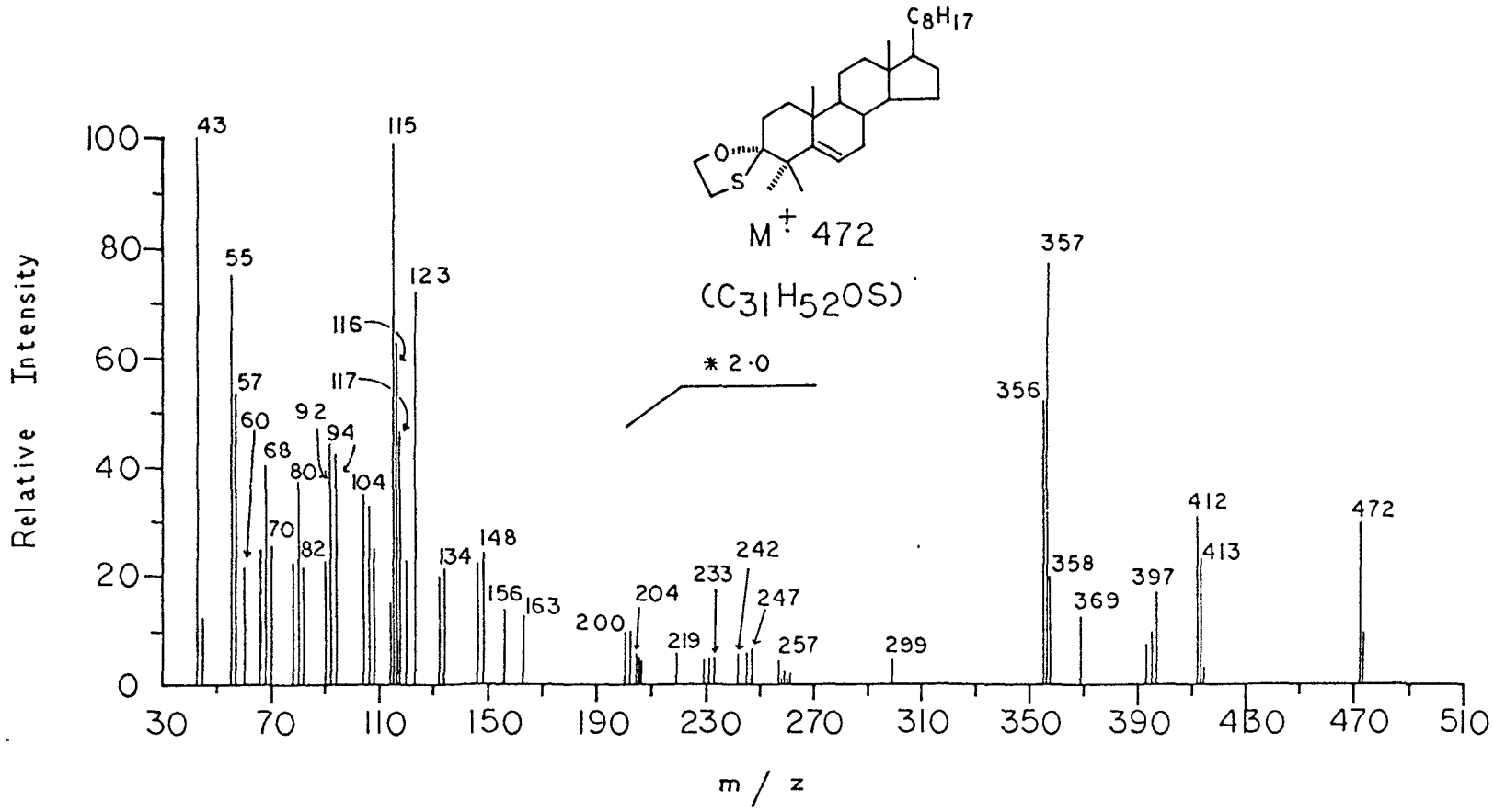
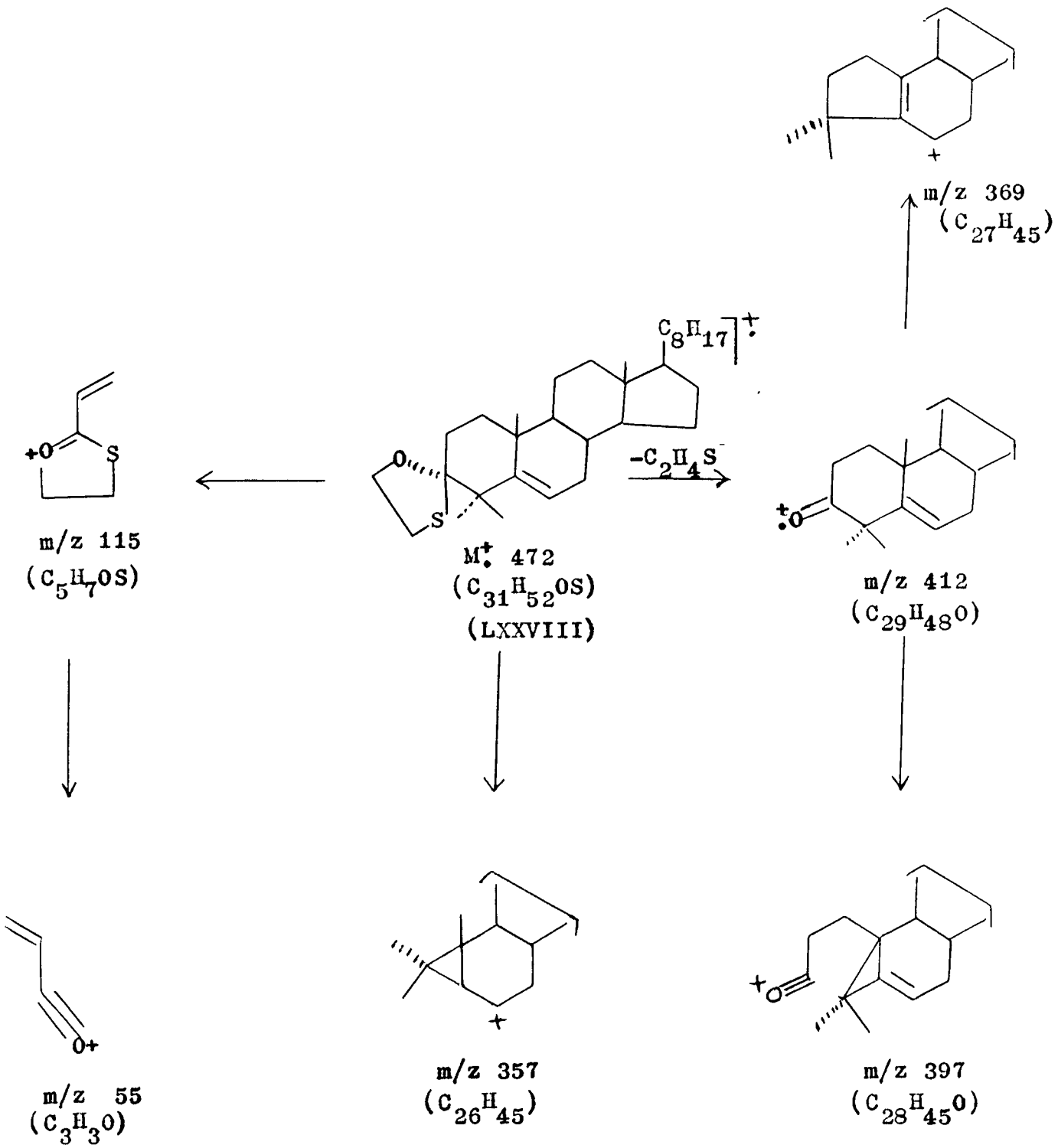


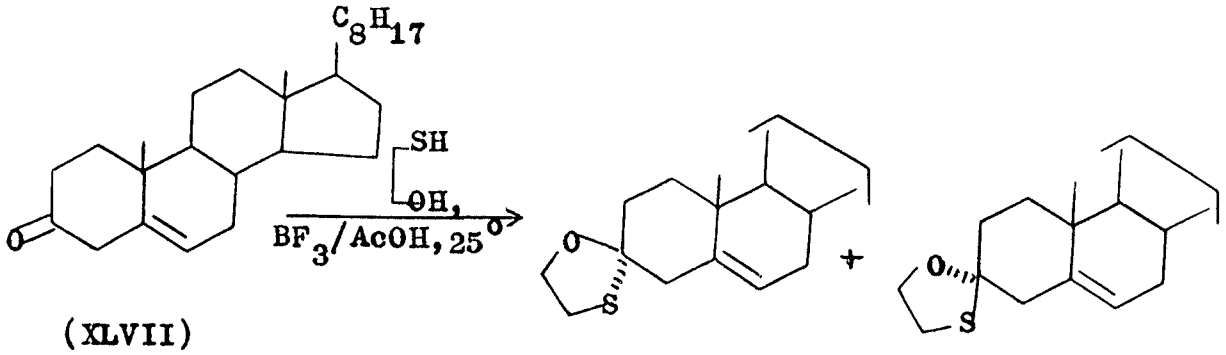
Fig. 2 Mass Spectrum of LXXVIII.

Scheme - 1

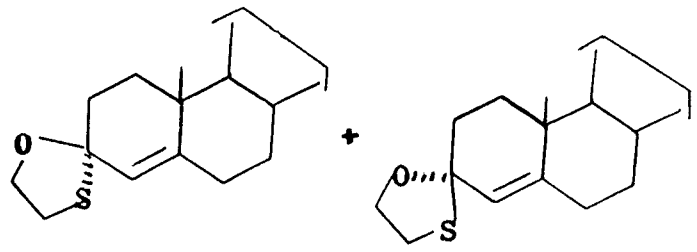

m/z 369
($C_{27}H_{45}$)
C_8H_{17}
$-C_2H_4S$
m/z 115
(C_5H_7OS)
M^+ 472
($C_{31}H_{52}OS$)
(LXXVIII)
m/z 412
($C_{29}H_{48}O$)
m/z 55
(C_3H_3O)
m/z 357
($C_{26}H_{45}$)
m/z 397
($C_{28}H_{45}O$)

Reaction of cholest-5-en-3-one (XLVII) with β -mercaptoethanol

The cholest-5-en-3-one (XLVII) was treated with β-mercaptoethanol in acetic acid (BF_3-etherate used as a catalyst). After the usual work up of reaction mixture and column chromatography over silica gel, compounds melting at 135°, 115°, 118° and a non crystallizable oil were obtained.



(XLVII) (LXXIX) (LXXX)



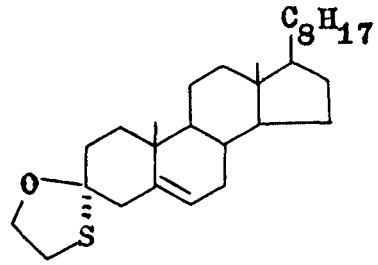
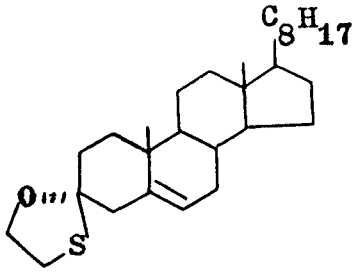
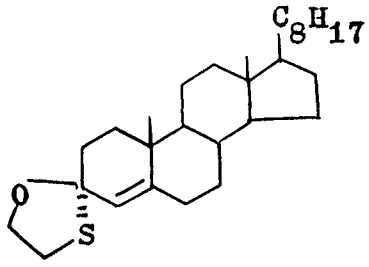
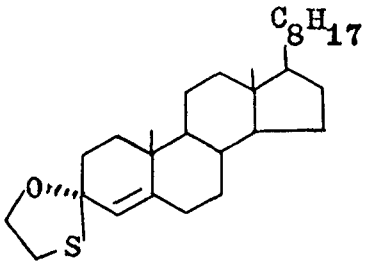
(LXXXI) (LXXXII)

Characterization of the compound, m.p. 135° as 3β-oxy, 3α-thiodimethylene cholest-5-ene (LXXVI); m.p. 115° as 3α-oxy, 3β-thiodimethylene cholest-5-ene (LXXIX); m.p. 118° as 3β-oxy, 3α-thiodimethylene cholest-4-ene (LXXX) and oil (LXXXI) as 3α-oxy, 3β-thiodimethylene-cholest-4-ene (LXXXII)

The compounds m.p. 135° (LXXIX), 115° (LXXX), 118° (LXXXI) and oil (LXXXII) were analysed correctly for $C_{29}H_{48}OS$ (positive nitroprusside test for sulphur). The molecular composition of all these compounds indicated that they were isomeric. The I.R. spectra of compounds (LXXIX-LXXII) exhibited bands at 1060, 1055, 1050 and 1045 cm^{-1} respectively for hemithioketal ring. The distinction between (LXXIX), (LXXX), (LXXXI) and (LXXXII) was made possible on the basis of their N.M.R. spectral data (Table - 1).

Table - 1

δ-Value and splitting pattern of $-OC\underline{H}_2$ and $-SC\underline{H}_2$ protons are tabulated as follows.

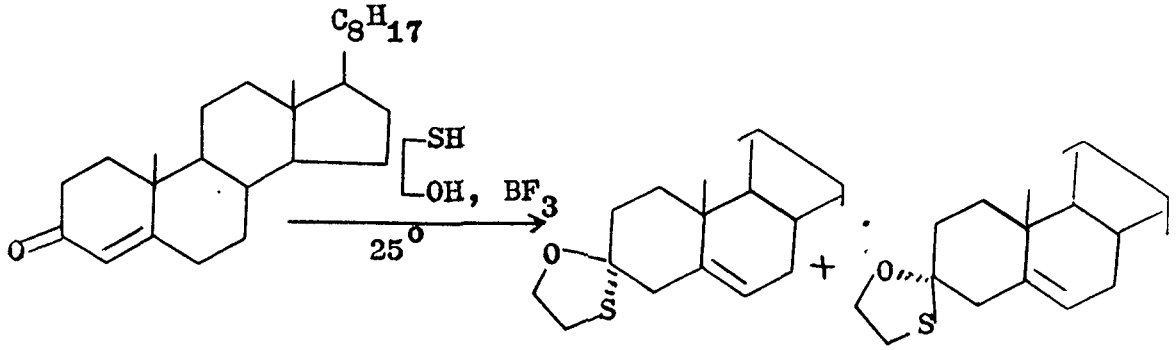
Compound	$-OC\underline{H}_2$	$-SC\underline{H}_2$	C6-H/C4-H
 (LXXIX)	4.2 distorted t	3.0t	5.4m
 (LXXX)	4.18 distorted t 4.0 distorted t	3.1dd	5.2m
 (LXXXI)	4.17 distorted t	2.64t	5.6s
 (LXXXII)	4.3 distorted t 3.8 distorted t	2.85dd	5.63s

The appearance of two distorted triplets and a double doublet in N.M.R. spectra of (LXXX) and (LXXXII) may be explained by assuming that the methylene protons bonded with the axially oriented oxygen atom, were magnetically non-equivalent (pseudo equatorial and pseudo axial). Thus they behave differently towards the applied field and appeared at different shifts in the N.M.R. as distorted triplets. The distortion in triplets may be considered due to the long range coupling. Methylene protons attached to the sulphur atom were almost magnetically equivalent and appeared as a double doublet by the splitting with pseudo equatorial and pseudo axial protons of $OC\underline{H}_2$. The appearance of two triplets in compounds (LXXIX) and (LXXXI) may be explained by assuming that $O-CH_2$ bonds in (LXXIX and LXXXI) were equatorially oriented and the methylene protons attached to the oxygen atom were almost magnetically equivalent and same for the methylene protons of $S-CH_2$ group, so the two triplets each integrating for two protons were due to the splitting of each other. The distortion in triplets of $O-CH_2$ might be considered due to the long range coupling.

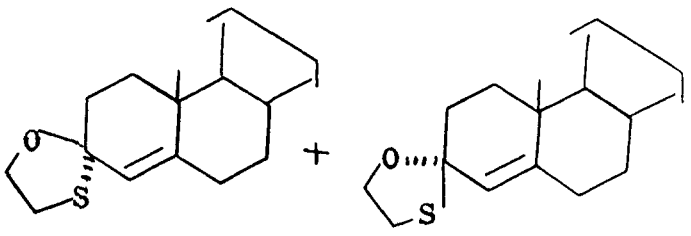
The splitting pattern of $O-CH_2$ and $S-CH_2$ protons were same in the compounds (LXXIX) and (LXXXI) but difference lies in the splitting of C4 and C6 vinylic protons which appeared as sharp singlet in (LXXXI) and as multiplet in (LXXIX). Subsequently compounds (LXXX) and (LXXXII) were differentiated on the basis of similar observations.

Reaction of cholest-4-en-3-one (LXXVI) with β -mercaptoethanol

The treatment of cholest-4-en-3-one (LXXVI) with β-mercaptoethanol in the usual manner as described for cholest-5-en-3-one (XLVII), afforded the compounds (LXXIX - LXXXII) which were found to be identical (IR, NMR, TLC and M.P.) with the compounds obtained from cholest-5-en-3-one (XLVII) under similar reaction conditions discribed earlier.



(LXXVI) (LXXIX) (LXXX)



(LXXXI) (LXXXII)

Experimental

All melting points were observed on a Kofler apparatus and are uncorrected. Infrared spectra (I.R.) were determined in nujol with a Perkin-Elmer 237 spectrophotometer. I.R. values are given in cm^{-1}. Nuclear Magnetic Resonance (N.M.R.) were run in $CDCl_3$ on a Varian A-60 instrument with tetramethyl silane (T.M.S.) as the internal standard. The N.M.R. values are given in ppm (δ). Mass spectra were recorded on JMSD-100 mass spectrometer at 70 eV. Thin layer chromatographic (TLC) plates were coated with silica gel (G) and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. Anhydrous sodium sulphate (Na_2SO_4) was used as the drying agent. The abbreviations "s, d, t, m and d,d" denote "singlet, doublet, triplet, multiplet and double doublet respectively.

3β-Hydroxy-5,6β-dibromo-5α-cholestane

To a solution of cholesterol (14 g) in ether (100 ml) was added gradually the bromine solution (9.6 g in 100 ml of glacial acetic acid containing 1 g of anhydrous sodium acetate). The solid thus obtained was filtered under suction and washed

with cold ether-acetic acid mixture (3:7). The dried dibromide (16 g) showed m.p. 113-114° (reported[17] m.p. 114°).

5,6β-Dibromo-5α-cholestan-3-one

3β-Hydroxy-5,6β-dibromo-5α-cholestane (10 g) was suspended in acetone (300 ml). The suspension was cooled to 0-5°. It was stirred for 5 min. and to this mixture Jones reagent was added dropwise over a period of 20 min. at the maintained temperature of 0-5°. Water (200 ml) was added and dibromoketone was filtered under suction, washed with water, methanol and air dried (9 g), m.p. 73-75° (reported[17] m.p. 73-75°).

Cholest-5-en-3-one (XLVII)

To a solution of 5,6β-dibromo-5α-cholestan-3-one (5 g) in ether (100 ml) was added glacial acetic acid (2.5 ml). Zinc dust (7.5 g) was added in small portions during 30 min. with continuous shaking. After complete addition, the ethereal solution containing zinc dust was filtered, washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate (anhydrous). Removal of the solvents provided an oil which was crystallized from methanol (3.3 g), m.p. 126-127° (reported[17] m.p. 129°).

Cholest-4-en-3-one (LXXVI)

Cholest-5-en-3-one (4 g) was dissolved in ethanol (40 ml) and to this was added a solution of oxalic acid (0.5 g) in ethanol (5 ml). The reaction mixture was refluxed for 15 min. then allowed to stand at room temperature. Crystallization started after 1 hr and to ensure complete crystallization, it was cooled at 0-4° and then filtered. The crude (LXXVI) was recrystallized from methanol (3 g), m.p. 80° (reported[17] m.p. 81-82°).

4,4-Dimethylcholest-5-en-3-one (LXXV)

Potassium (0.3 g; 3 mole equivalent) was dissolved in dry t-butyl alcohol (10 ml) and the resultant solution was added to a boiling solution of cholest-4-en-3-one (10 g) in benzene (30 ml). Methyl iodide (3 ml) in benzene (30 ml) was then added dropwise and refluxing was continued for 25 min. The solution was allowed to cool down, water (5 ml) was added to this and the solvent was evaporated to dryness under reduced pressure. The dried mass was taken in ether and the insoluble potassium iodide was separated on filtration. The ethereal layer was washed with water, and dried over sodium sulphate (anhydrous). An oil was obtained on evaporation

of the solvent which was chromatographed over a column of silica gel (150 g). Elution with light petroleum yielded (LXXV) (2 g) which was crystallized from methanol m.p. 173° (reported[18] m.p. 172-174°).

Reaction of 4,4-dimethyl cholest-5-en-3-one (LXXV) with β-mercaptoethanol: 3β-Oxy, 3α-thiodimethylene, 4,4-dimethyl cholest-5-ene (LXXVII) and 3α-oxy, 3β-thiodimethylene, 4,4-dimethylcholest-5-ene (LXXVIII)

A mixture of 4,4-dimethylcholest-5-en-3-one (LXXV) (2.0 g) in dry benzene (100 ml) and β-mercaptoethanol (5 ml) (a few crystals of p-toluenesulphonic acid as catalyst) was refluxed for 10 hours. The reaction mixture was filtered. The filtrate was washed with water, sodium bicarbonate solution and dried over sodium sulphate (anhydrous). The residue obtained after evaporation of the solvent was chromatographed over silica gel (40 g). Elution with light petroleum gave (LXXVII) (150 mg), recrystallized from light petroleum, m.p. 130°C. (Found: C, 78.71; H, 11.11. $C_{31}H_{52}OS$ requires C, 78.81; H, 10.01%).

I.R. : ν max. 1640 (C=C), 1045 (hemithioketal ring), 1220 ($S-CH_2$), 1150 and 1088 cm^{-1} (C-O).

N.M.R.: δ 5.5m (C6-H), 4.2 distorted t (OCH_2), 2.9t (SCH_2), 1.1 (C10-CH_3), 0.66 (C13-CH_3), 1.25, 0.9 and 0.80 (other methyl protons).

MS : M^+ 472.

Further elution with light petroleum yielded compound (LXXVIII) (130 mg), recrystallized from light petroleum, m.p., 140° (Found: C, 78.65; H, 11.17. $C_{31}H_{52}OS$ requires C, 78.81; H, 11.01%).

I.R. : ν max. 1635 (C=C), 1060 (hemithioketal ring), 1220 ($S-CH_2$), 1149 and 1090 cm^{-1} (C-O).

N.M.R.: δ 5.5m (C6-$\underline{H}$), 4.3, 4.0 distorted ts ($OC\underline{H}_2$), 2.83, d,d ($S-C\underline{H}_2$), 1.1 (C10-$C\underline{H}_3$), 0.66 (C13-$C\underline{H}_3$), 1.2, 0.90 and 0.80 (other methyl protons).

MS : M^+ 472.

<u>Reaction of cholest-5-en-3-one (XLVII) with β-mercaptoethanol: 3β-Oxy,3α-thiodimethylenecholest-5-ene (LXXIX), 3α-oxy, 3β-thiodimethylenecholest-5-ene (LXXX), 3β-oxy,3α-thiodimethylenecholest-4-ene (LXXXI) and 3α-oxy-3β-thiodimethylenecholest-4-ene (LXXXII)</u>

The cholest-5-en-3-one (XLVII) (2.0 g) was treated with β-mercaptoethanol (5 ml) and BF_3-etherate (1 ml) in acetic acid (100 ml) and the mixture was left at room temperature for 2 hours. The solution was diluted with methanol and was poured into water and extracted with ether. The oil residue obtained after evaporation of the solvent was chromatographed over silica gel (40 g). Elution with

light petroleum:ether (20:1) gave (LXXIX) which was recrystallized from light petroleum (30 mg), m.p. 135°. (Found: C, 78.29; H, 10.89. $C_{29}H_{48}OS$ requires C, 78.37; H, 10.81%).

I.R.: ν max. 1638 (C=C), 1060 cm^{-1} (hemithioketal ring).

N.M.R.: δ 5.4 m (C6-$\underline{H}$), 4.2 distorted t (O$C\underline{H}_2$), 3.0 t (S$C\underline{H}_2$), 1.01 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.91 and 0.81 (other methyl protons).

Continued elution with light petroleum:ether (20:1) gave (LXXX) which was recrystallized from light petroleum (35 mg), m.p. 115°C. (Found: C, 78.41; H, 10.78. $C_{29}H_{48}OS$ requires: C, 78.37; H, 10.81%).

I.R. : ν max. 1635 (C=C), 1055 cm^{-1} (hemithioketal ring).

N.M.R.: δ 5.2 m (C6-$\underline{H}$), 4.18, 4.0 distorted ts (-O-$C\underline{H}_2$), 3.0 d,d (-S-$C\underline{H}_2$), 1.01 (C10-$C\underline{H}_3$), 0.69 (C13-$C\underline{H}_3$), 0.93 and 0.83 (other methyl protons).

Further elution with light petroleum:ether (5:1) yielded compound (LXXXI), recrystallized from light petroleum (40 mg), m.p. 118°C. (Found: C, 78.45; H, 10.75. $C_{29}H_{48}OS$ requires C, 78.37; H, 10.81%).

I.R. : ν max. 1636 (C=C), 1050 cm^{-1} (hemithioketal ring).

N.M.R.: δ 5.6s (C4-$\underline{H}$), 4.17 distorted t (O$C\underline{H}_2$), 2.64t(S$C\underline{H}_2$),

1.02 (C10-C$\underline{H}_3$), 0.75 (C13-C$\underline{H}_3$), 0.93 and 0.83 (other methyl protons).

Elution with light petroleum:ether (1:1) gave a noncrystallizable oil(LXXXII) (40 mg). (Found: C, 78.33; H, 10.86. $C_{29}H_{48}OS$ requires: C, 78.37; H, 10.81%).
I.R. : ν max. 1640 (C=C), 1045 cm^{-1} (hemithioketal ring).
N.M.R.: δ 5.63s (C4-$\underline{H}$), 4.3, 3.8 distorted ts (OC$\underline{H}_2$), 2.85 d,d (SC$\underline{H}_2$), 1.01 (C10-C$\underline{H}_3$), 0.75 (C13-C$\underline{H}_3$), 0.9 and 0.83 (other methyl protons).

Reaction of cholest-4-en-3-one (LXXVI) with β-mercaptoethanol

The cholest-4-en-3-one (2.0 g) was treated with β-mercaptoethanol (5 ml) and BF_3-etherate (1 ml) in acetic acid (100 ml) and left at room temperature for 2 hours. Usual worked up as described for (XLVII) gave the compounds m.p. 135°C (30 mg), 115°C (35 mg), 118°C (45 mg) and a noncrystallizable oil (40 mg) which were found identical in all respects to compounds (LXXIX), (LXXX), (LXXXI) and (LXXXII) obtained earlier with ketone (XLVII).

The mass spectra were measured on a Varian Jeol-D100 mass spectrometer at 70 eV using a direct insertion technique at source temperature of about 250°C.

The value (m/z) of the fragment ion from compounds were tabulated below. The value in parentheses are the relative abundance (%) of the peaks with respect to base peak as 100%.

3β-Oxy, 3α-thiodimethylene, 4,4-dimethyl cholest-5-ene (LXXVII)

M^{+} 472 (32.00; $C_{31}H_{52}OS$), m/z 413 (5.00), 412 (15.00), 398 (2.00), 397 (7.00), 369 (5.00), 358 (15.00), 357 (55.00), 356 (30.00), 300 (1.00), 163 (11.00), 161 (10.00), 159 (13.00), 152 (7.00), 151 (5.00), 150 (3.00), 124 (3.00), 117 (5.00), 116 (6.00), 115 (100), 55 (5.00), 45 (5.00).

3α-Oxy, 3β-thiodimethylene, 4,4-dimethyl cholest-5-ene (LXXVIII)

M^{+} 472 (30.00; $C_{31}H_{52}OS$), 414 (3.00), 413 (23.50); 412 (31.00), 397 (17.00), 395 (10.00), 393 (7.00), 369 (13.00), 358 (20.00), 257 (77.50), 355 (52.00), 299 (5.00), 261 (2.00), 260 (1.50), 259 (3.00), 258 (1.00), 257 (5.00), 247 (7.00), 245 (6.00), 242 (6.00), 233 (5.00), 231 (5.00), 229 (5.00), 219 (6.00), 206 (5.00), 205 (5.00), 204 (6.00), 202 (10.00),

200 (10.00), 163 (12.00), 156 (14.00), 148 (24.00), 146 (22.50), 134 (21.00), 132 (20.00), 123 (72.00), 120 (23.00), 117 (47.00), 116 (63.00), 115 (99·8), 108 (25.00), 106 (32.00), 104 (35.00), 94 (42.00), 92 (32.00), 82 (21.00), 80 (37.00), 78 (22.00), 70 (25.00), 68 (40.00), 60 (21.00), 57 (53.00), 55 (75.00), 43 (100).

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PART THREE

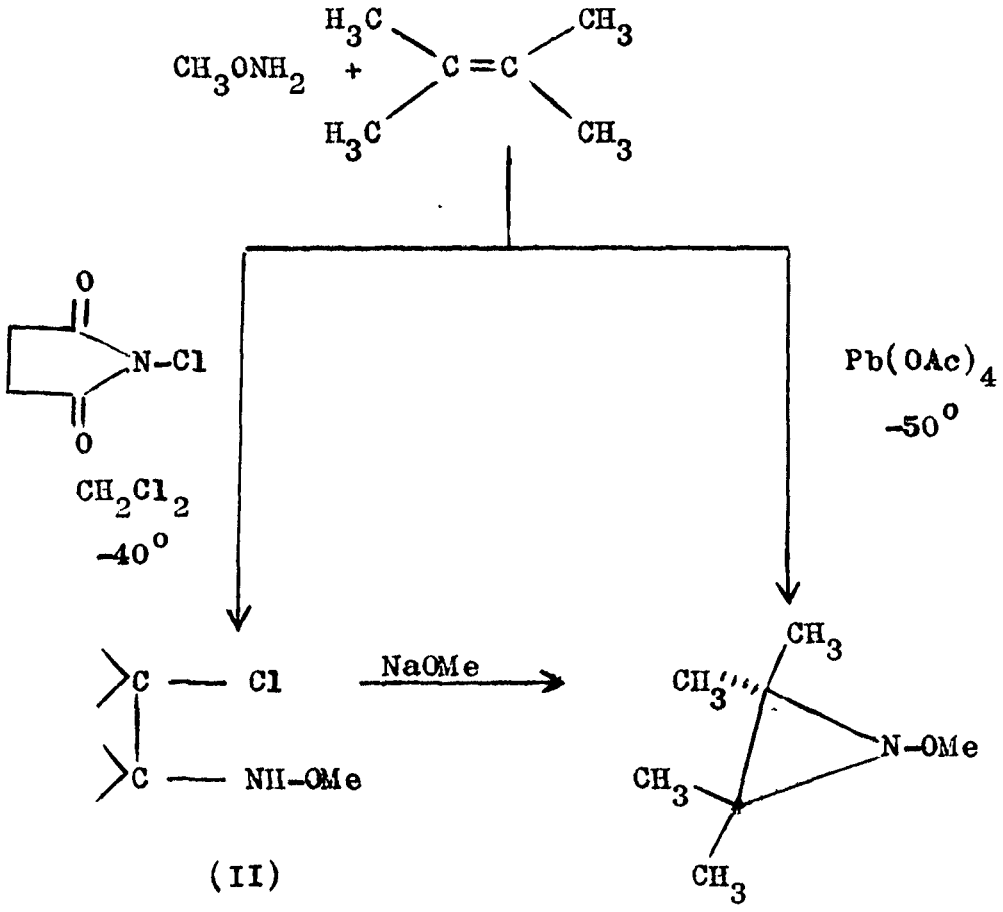
Synthesis of Steroidal Aziridines

Theoretical

The stereo chemical study of three membered ring with their highly compressed bond angles has long intrigued the organic chemists. These strained organic cyclic compounds have propensity towards ring opening. In fact the ability of aziridinium salts to undergo facile ring opening by nucleophiles can be used to explain the action of aziridines and of related β-haloamines as carcinostates, possibly by alkylating enzyme sites. Thus "Fenesterin" and ester of cholesterol containing the β-haloamine moiety have shown favourable carcinostatic activity in a number of tumor systems[1]. In connection with our work on stereospecific introduction of nitrogen containing functions into the steroid nucleus, we were interested in the synthesis of fused steroidal aziridines.

Several papers dealing with the synthesis of aziridines have appeared. The present chapter deals with some of the recent pertinent examples of the aziridines preparations. Boris[2] oxidised methoxyamine with lead tetra acetate in the presence of excess tetra methyl ethylene at -50° and obtained 1-methyl-2,2,3,3-tetra methyl aziridine (I). When the

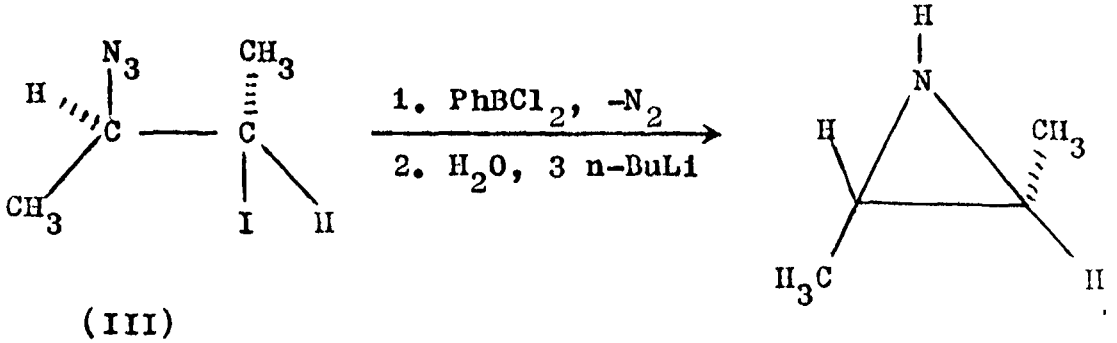
reaction was repeated with N-chlorosuccinimide in methylene chloride at -40^{o} hydroxylamine (II) was obtained which afforded the aziridine (I) on cyclization with sodium methoxide.



(II)

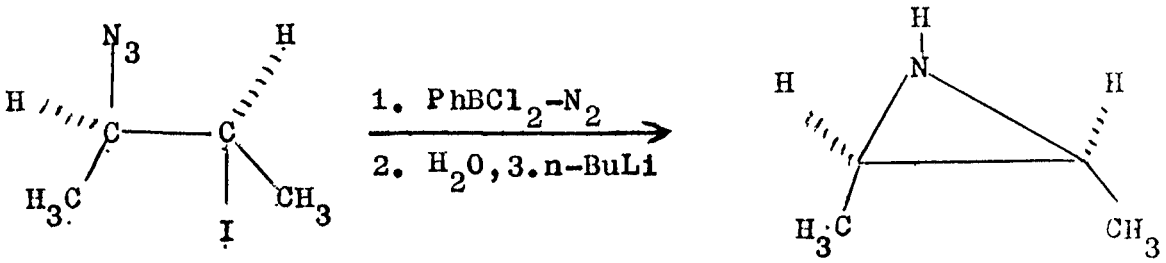
(I)

Levy et al.[3] reported the synthesis of N-phenyl aziridine (V) and (VI) from 1-azido-2-iodoethane (III) and (IV) as follows



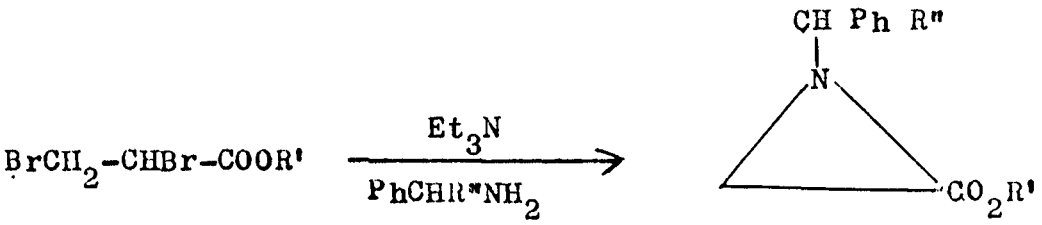
(III)

(V)



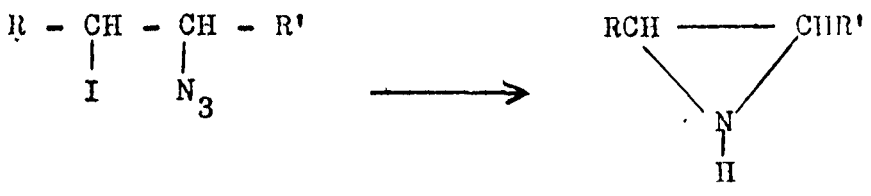
(IV) (VI)

Harada et al.[4] synthesized 1-alkylaziridine-2-carboxylates (VIIa-d) from the alkyl α ,β-dibromopropionates in the presence of chirol benzylamine.



	R'	R"
(VII-a)	Me	Me or Et
-b	Et	Me or Et
-c	Pr^i	Me or Et
-d	Bu^t	Me or Et

Hassner et al.[5] reported the aziridine formation by selective reduction of the azide function followed by the base catalysed ring closer (Table - 1).



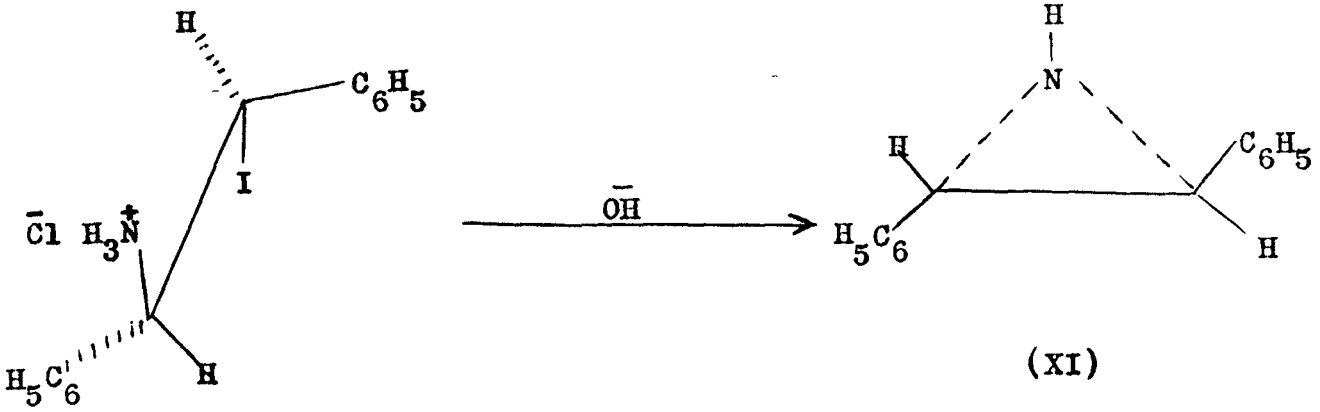
(VIII) (IX)

Table - 1

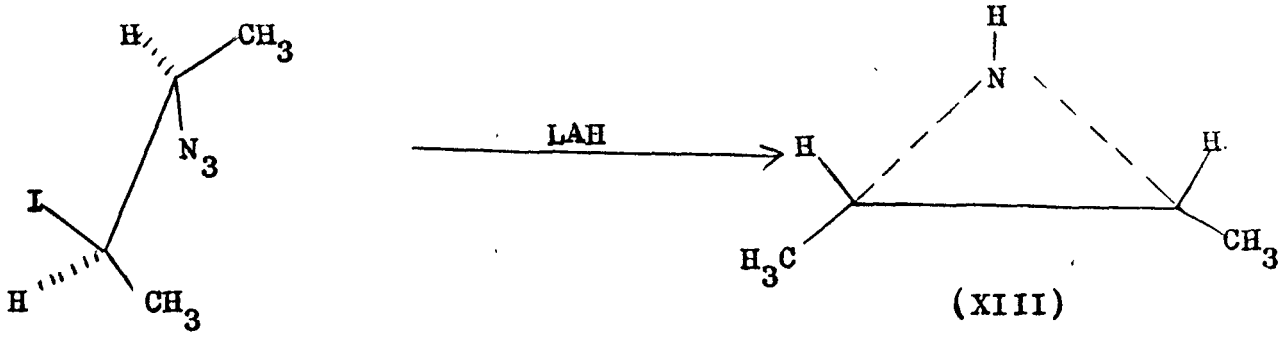
Reduction of 1,2-disubstituted 1-azido-2-iodo-ethane with lithium aluminium hydride

Iodoazides	R	R'	% of aziridines
(VIII)-a (Threo)	C_6H_5	C_6H_5	53 (Cis)
-b (Erythro)	CH_3	CH_3	11 (Trans)
-c (Threo)	CH_3	CH_3	100 (Cis)
-d (Erythro)	C_2H_5	C_2H_5	100 (Trans)
-e (Erythro)	1-pr	i-pr	95 (Trans)
-f (Erythro)	C_6H_5	CH_3	95 (Trans)
-g (Trans)	$(CH_2)_3$	$(CH_2)_3$	100
-h (Trans)	$(CH_2)_4$	$(CH_2)_4$	100
-i (Trans)	$(CH_2)_5$	$(CH_2)_5$	100

Trans-diphenyl aziridine (II) was obtained by base catalysed hydrolysis of erythro-1-amino-2-iodo-1,2-diphenyl ethane hydrochloride (X), while threo-2-azido-3-iodobutane (XII) gave cis-2,3-dimethylaziridine (XIII)[5] under the same reaction conditions.

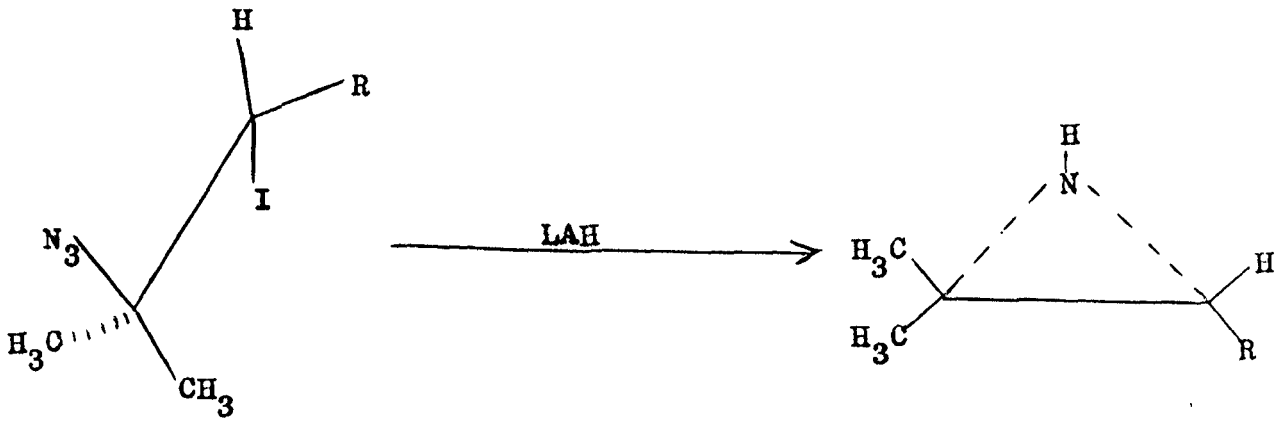


(X) (XI)



(XII) (XIII)

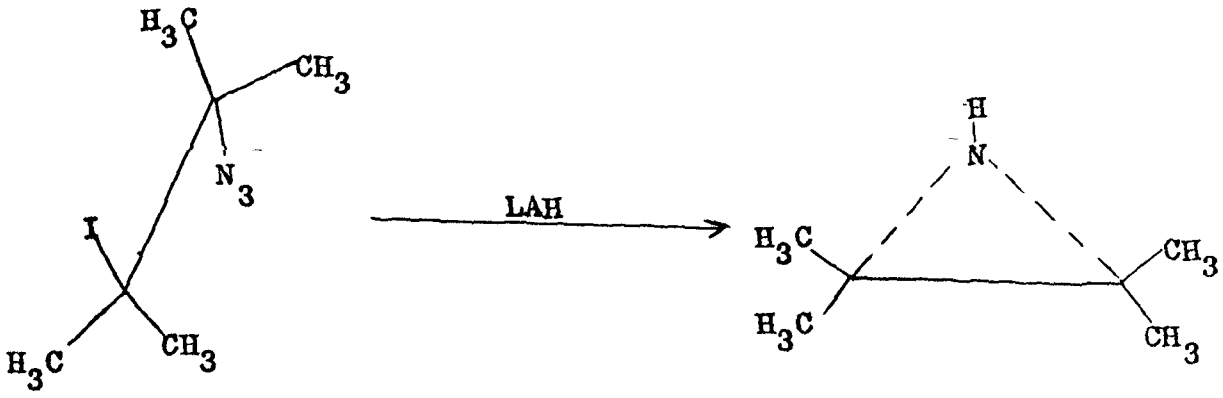
(XII) The alkylethylene adducts (XIV) and (XV) gave 3-methyl and 3-ethyl-2,2-dimethyl aziridines (XVI) and (XVII) under similar reaction conditions.[5]



	R
(XIV)	CH_3
(XV)	C_2H_5

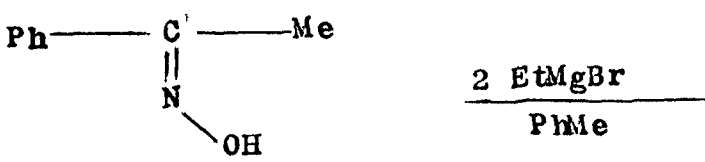
	R
(XVI)	CH_3
(XVII)	C_2H_5

The iodoazide (XVIII) on lithium aluminium hydride reduction provided 2,2,3,3-tetramethyl aziridine (XIX)[5].

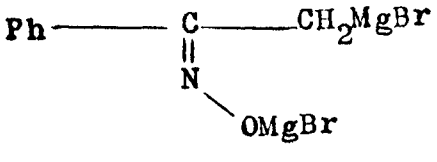


(XVIII) (XIX)

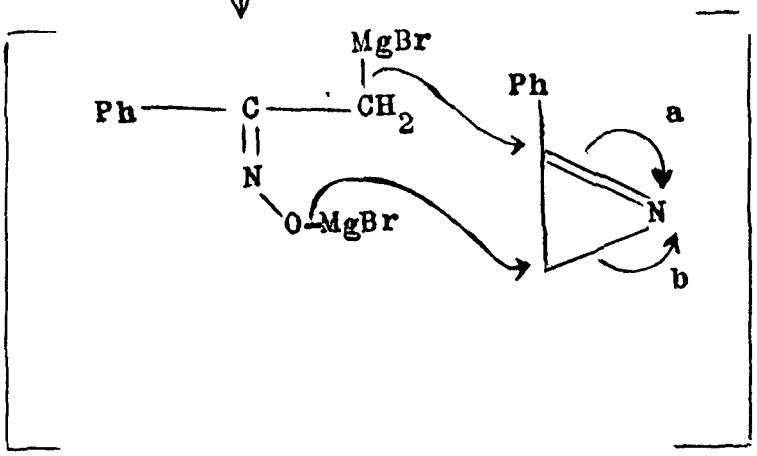
Recently Laurent et al.[6] reported the synthesis of secondary aziridine by the Hoch Compbell reaction (from an oxime with Grignard reagent in toluene) which has found many applications and various cyclization mechanisms have been proposed. However, the nature of the intermediates has not been established.

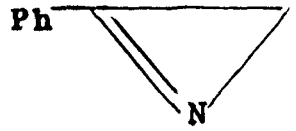


(XX)

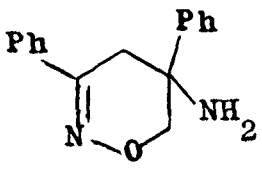


(XXI)

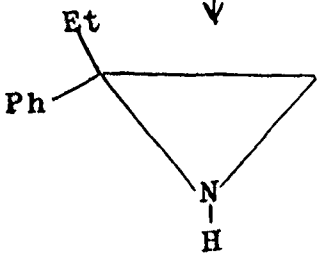




(XXII)

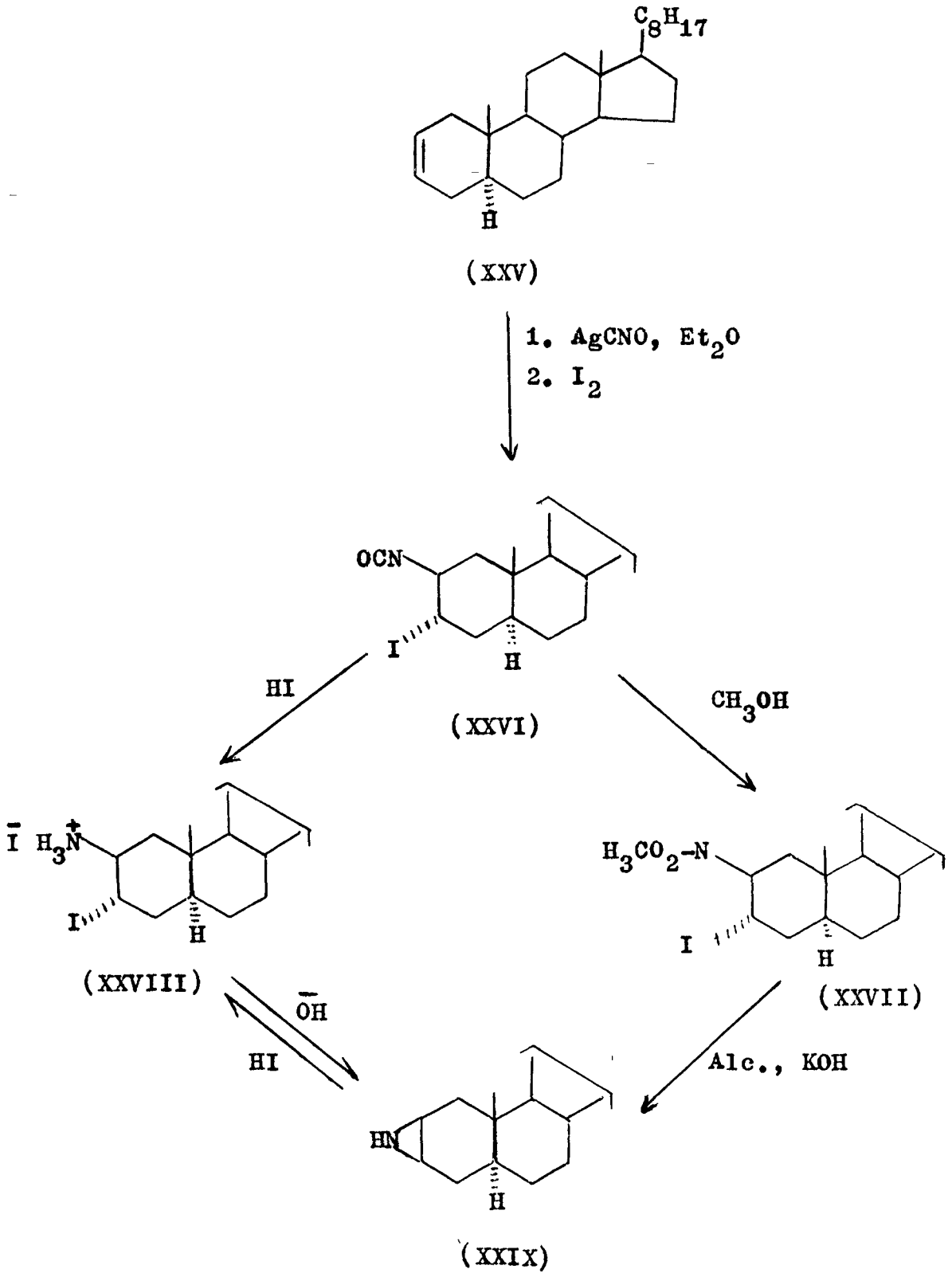


(XXIV)

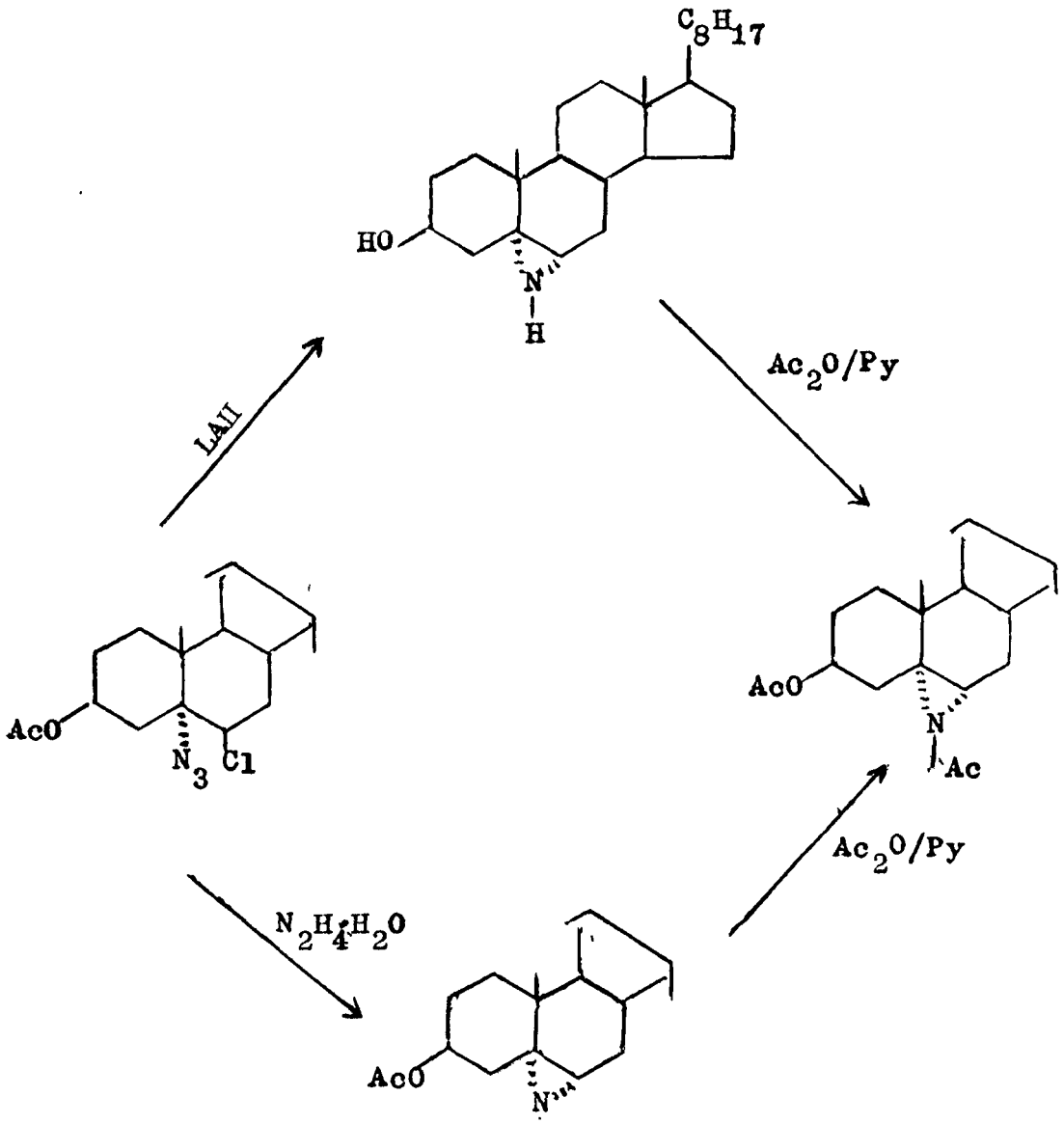


(XXIII)

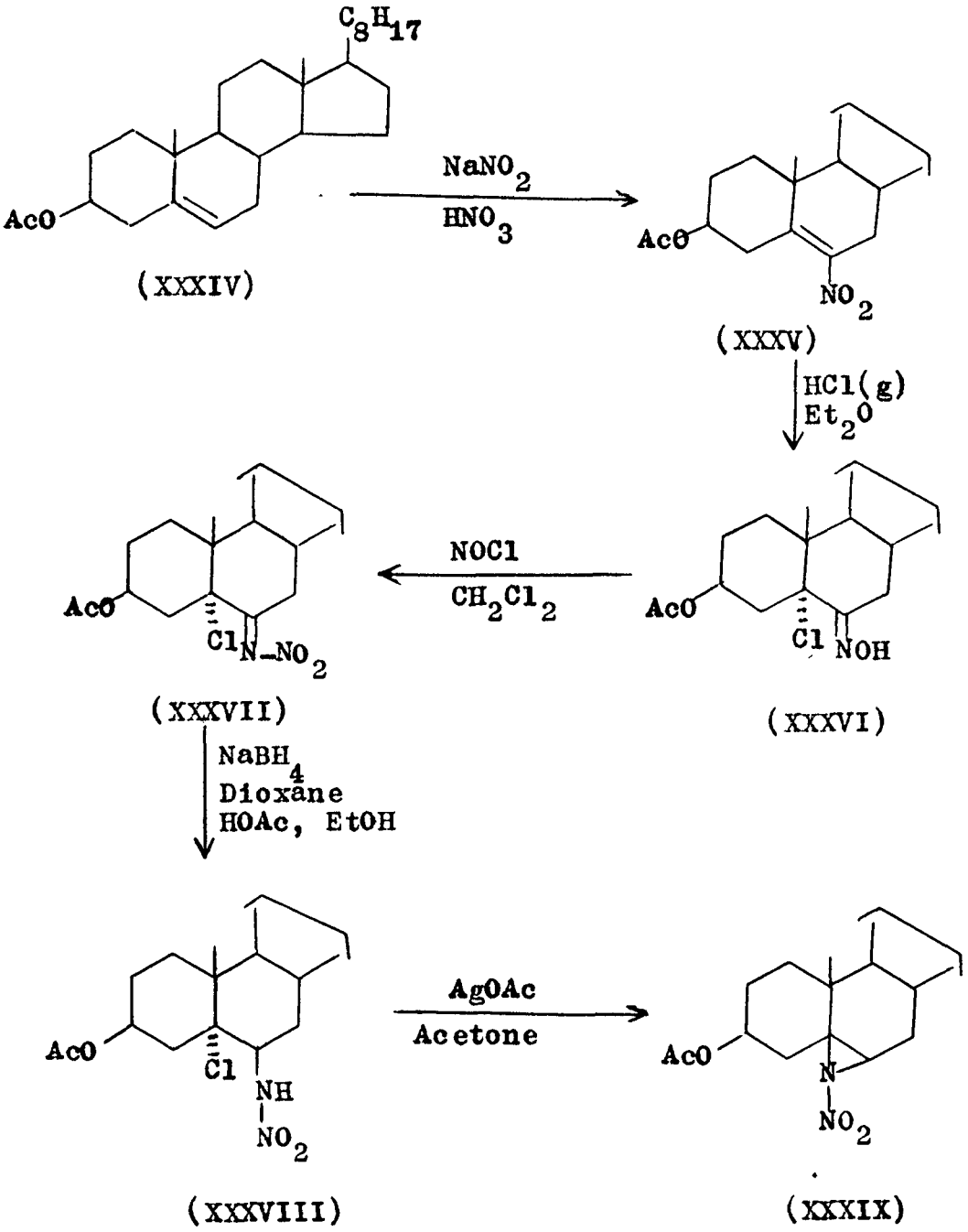
Hassner et al.[7] reported the synthesis of steroidal aziridine (XXIX) according to the scheme given below.



Snatzke et al.[8] prepared N-acetoxy aziridine (XXXIII) from (XXX) according to the reaction sequence given below.

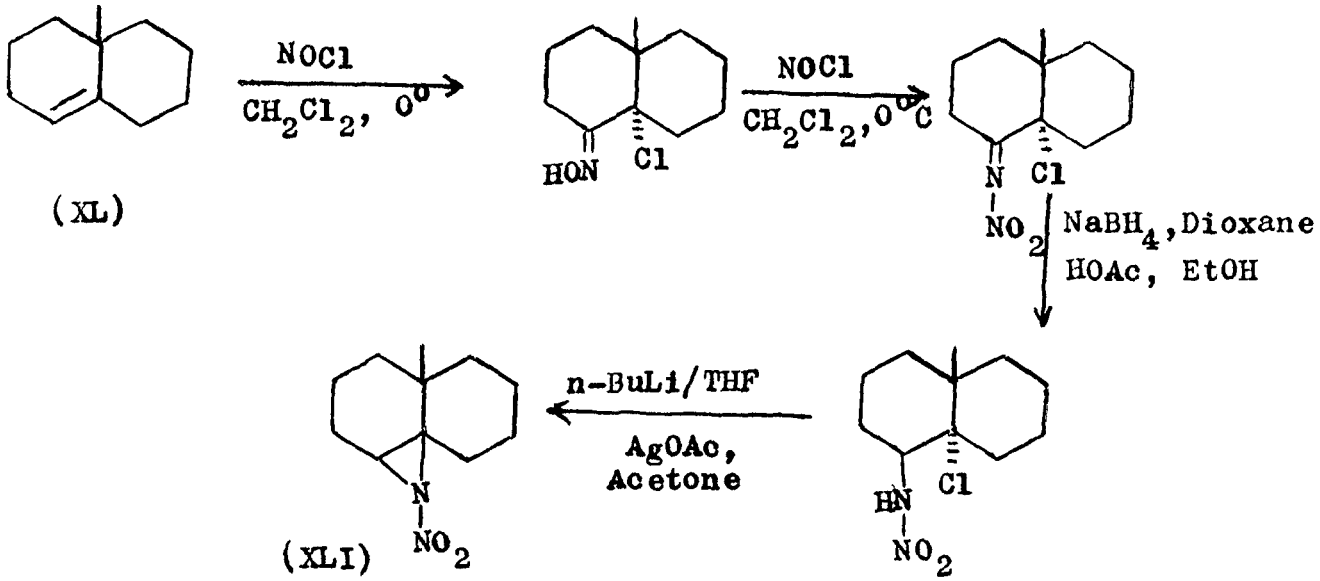


Hair et al.[9] reported the formation of N-nitroaziridine (XXXIX) starting from 3β-acetoxycholest-5-ene (XXXIV) as follows.



(XXXIV) (XXXV) (XXXVI) (XXXVII) (XXXVIII) (XXXIX)

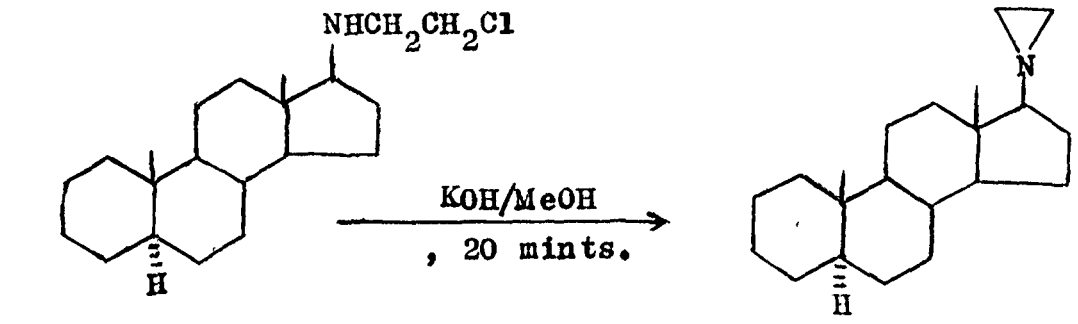
Similarly 10-methyl- $\Delta^{1,9}$-decalin (XL) provided 10-methyl-1,9 (N-nitroaziridine) decalin (XLI).



(XL)

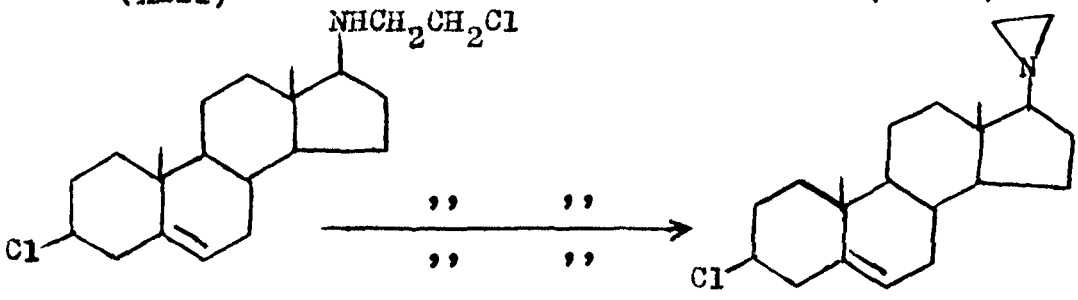
(XLI)

A number of aziridines have been synthesized by Langlois et al.[10] treating β-chloroamines with methanolic potassium hydroxide.



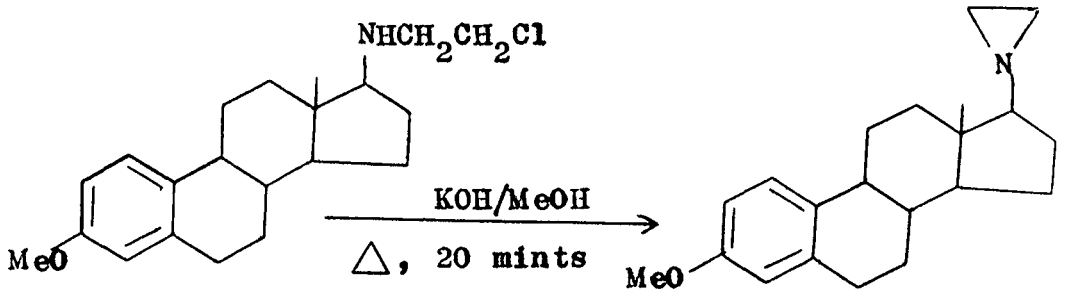
(XLII)

(XLIII)



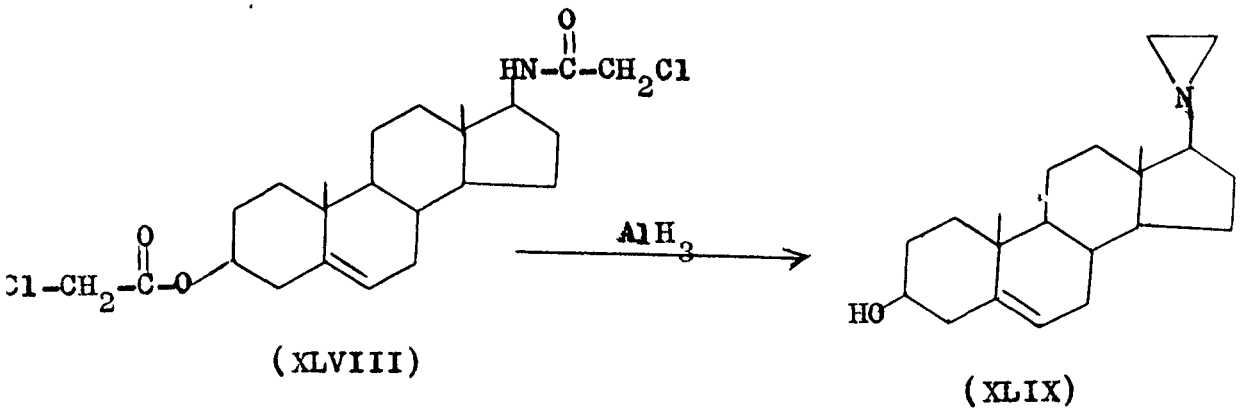
(XLIV)

(XLV)

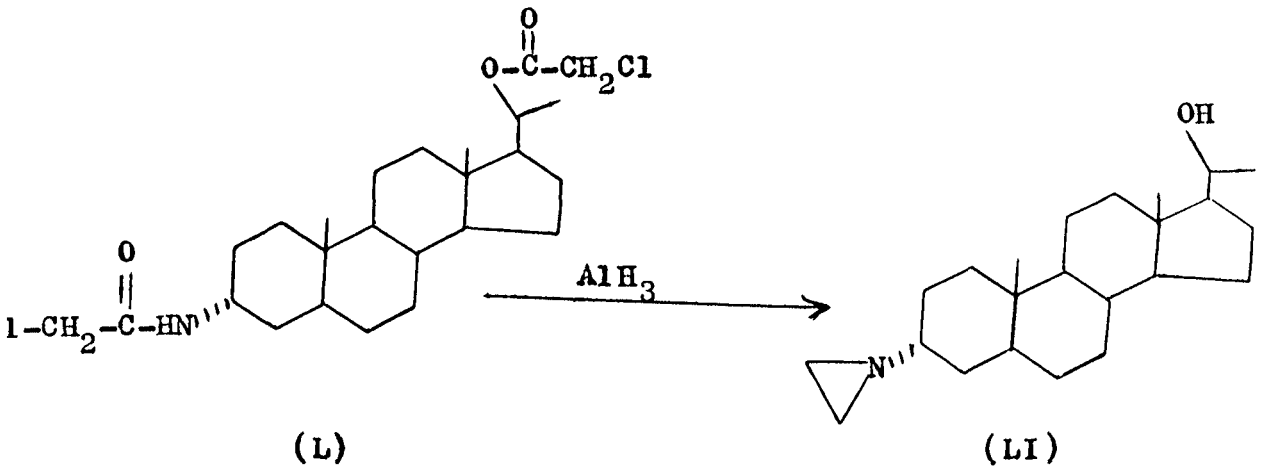


(XLVI) (XLVII)

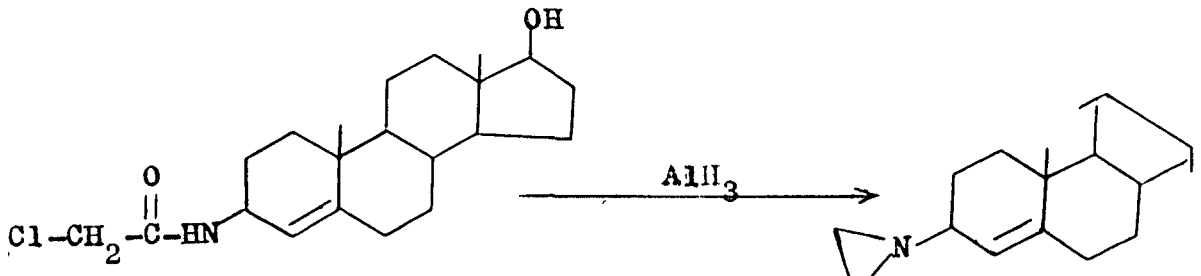
The chloro acetamides (XLVIII-LVI) on aluminium hydride reduction provided the corresponding aziridines (XLIX-LVII).



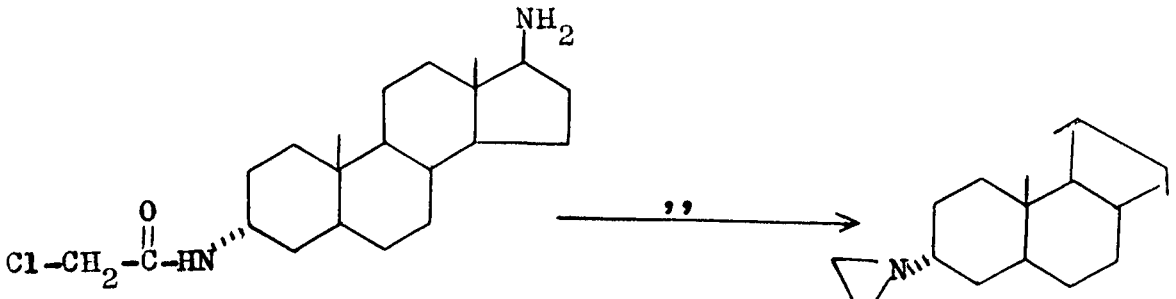
(XLVIII) (XLIX)



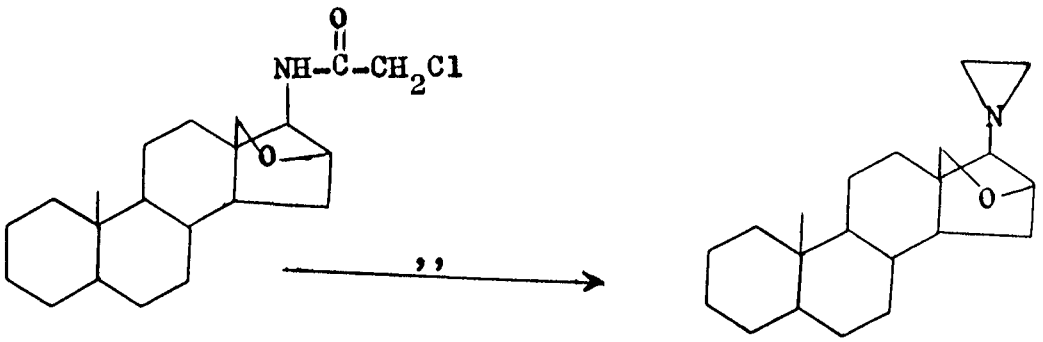
(L) (LI)



(LII) (LIII)

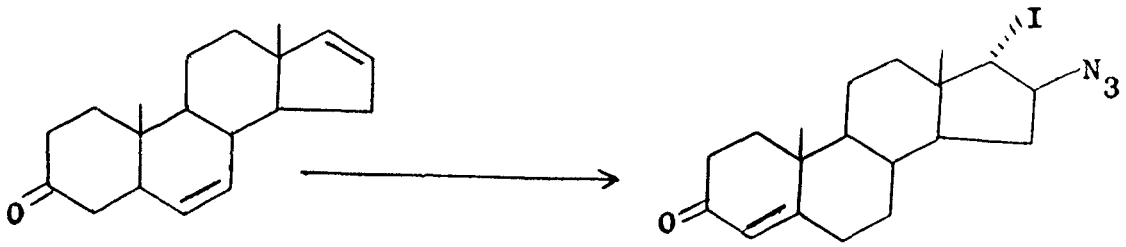


(LIV) (LV)

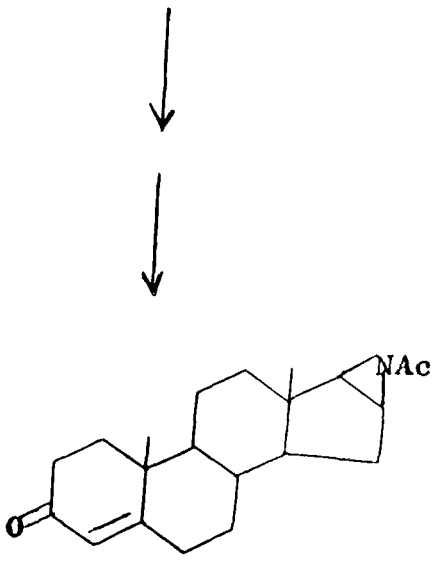


(LVI) (LVII)

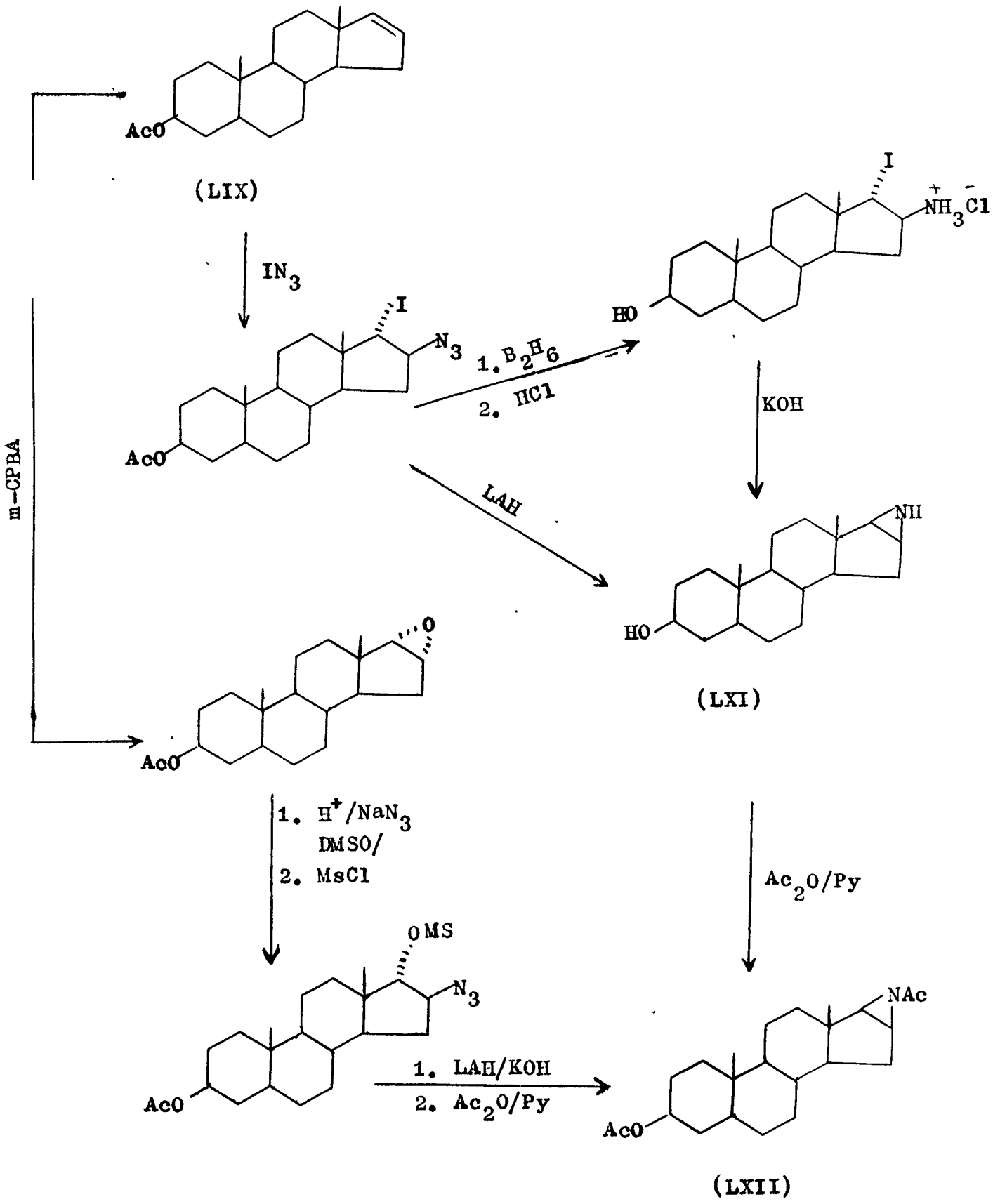
Gary et al.[11] reported the synthesis of aziridines (LX, LXI, LXII) from $\Delta^{6,16}$-androstadien-3-one (LVIII) and 3β-acetoxy-16-androstene (LIX) according to the scheme given below.



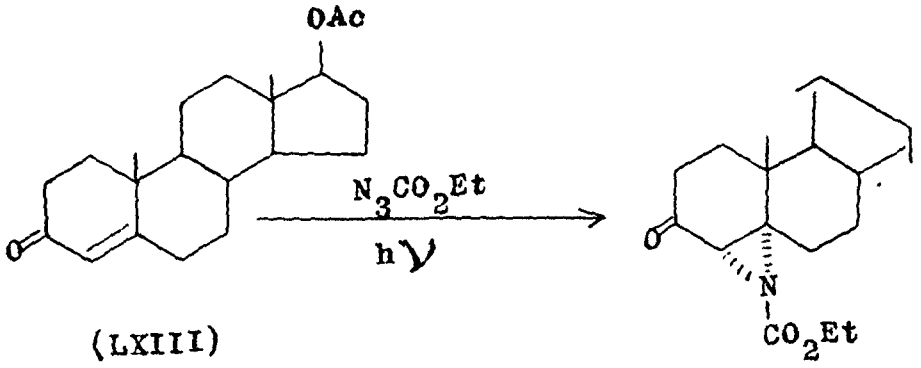
(LVIII)



(LX)

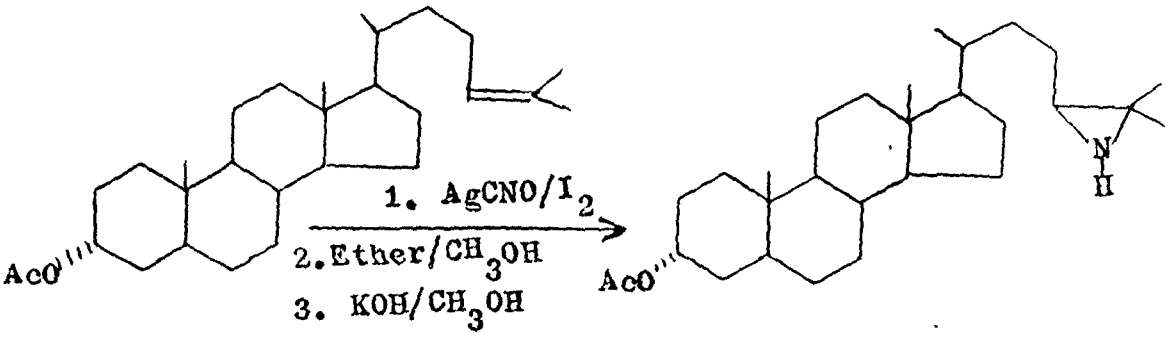

AcO
(LIX)
IN3
I
N3
AcO
1. B2H6
2. HCl
HO
I
NH3Cl
KOH
LAH
NH
HO
(LXI)
m-CPBA
O
AcO
1. H+/NaN3
DMSO/
2. MsCl
OMS
N3
AcO
1. LAH/KOH
2. Ac2O/Py
Ac2O/Py
NAc
AcO
(LXII)

It has been reported that the mixture of testosterone acetate (LXIII) and ethyl azido formate on irradiation yielded the aziridine (LXIV).[12]

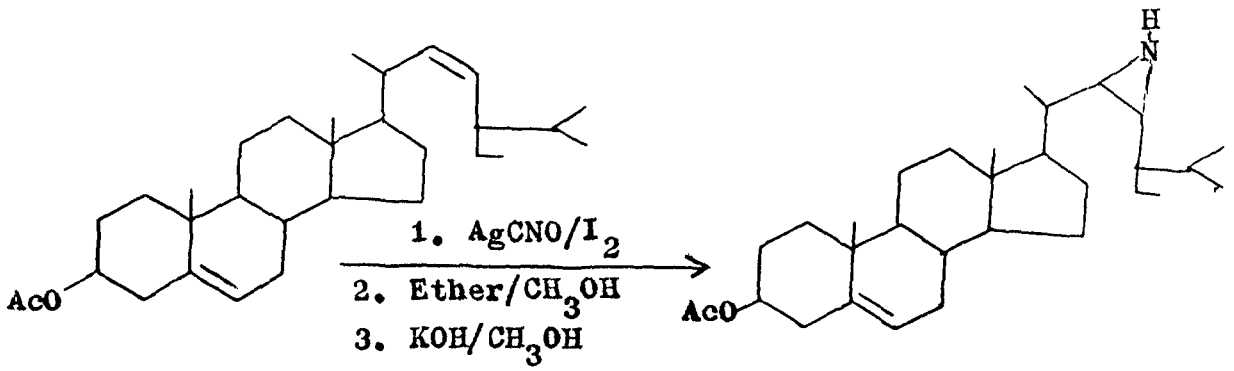


(LXIII) (LXIV)

Ikan et al.[13] converted desmostanyl 3α-acetate (LXV-a) into the aziridine (LXVI). Analogous sequence of reactions led to the formation of aziridine (LXVII) from stigmasteryl acetate (LXV-b).

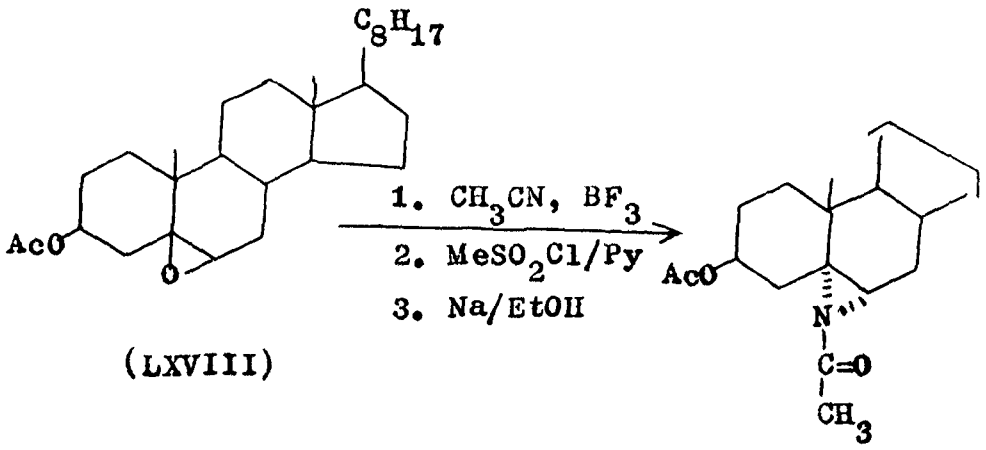


(LXV-a) (LXVI)



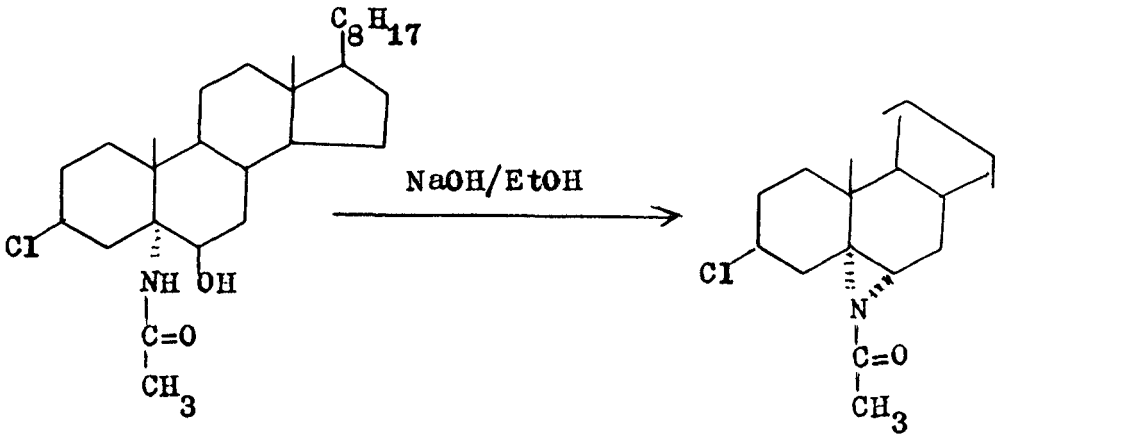
(LXV-b) (LXVII)

Ducker et al.[14] reported the formation of ∝-aziridine (LXIX) from the β-epoxide (LXVIII) via Ritter reaction.



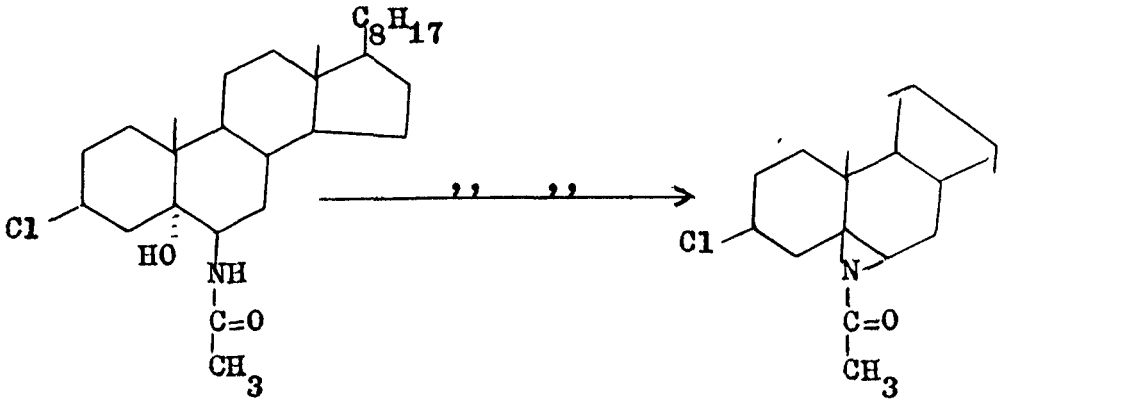
(LXVIII) (LXIX)

It was reported that the treatment of 3β-chloro-5-acetylamino-6β-hydroxy-5α-cholestane (LXX) and 3β-chloro-5-hydroxy-6β-acetylamino-5α-cholestane (LXXI) with alcoholic solution of sodium hydroxide provided aziridines (LXXII-α) and (LXXIII-β) respectively.[15]



(LXX)

(LXXII)

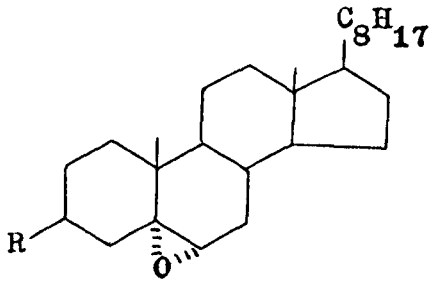


(LXXI)

(LXXIII)

Discussion

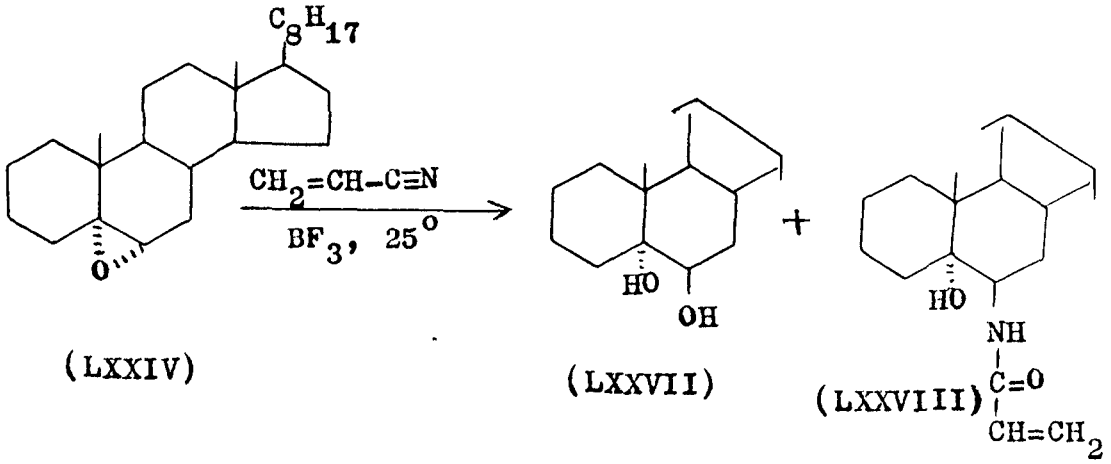
Among the organic compounds which were found to exhibit carcinostatic activity, the aziridine and the related β -haloethylamine have maintained an outstanding place. The present work describes the synthesis of aziridines derived from hitherto unexplored steroidal α-epoxides such as 5,6α-epoxy-5α-cholestane (LXXIV), 3β-acetoxy-5,6α-epoxy-5α-cholestane (LXXV) and 3β-chloro-5,6α-epoxy-5α-cholestane (LXXVI).



	R
(LXXIV)	H
(LXXV)	OAc
(LXXVI)	Cl

Reaction of 5,6α-epoxy-5α-cholestane (LXXIV) with acrylonitrile-borontrifluoride etherate

Borontrifluoride etherate (as catalyst) was added dropwise over a period of 15 minutes to a stirred suspension of 5,6α-epoxy-5α-cholestane (LXXIV) in acrylonitrile at room temperature. After work up of the reaction mixture, the residue obtained was chromatographed over silica gel. Two solid compounds having m.p. 124° and 195° were obtained.



(LXXIV) (LXXVII) (LXXVIII)

Characterization of the compound, m.p. 124° as 5,6β-dihydroxy-5α-cholestane (LXXVII)

The compound, m.p. 124° (reported[16] m.p. 125.5°) was correctly analysed for $C_{27}H_{48}O_2$. The molecular composition showed the addition of one oxygen atom to the substrate (LXXIV). The I.R. spectrum exhibited absorption band at

3400 cm^{-1} (OH). No other significant bands were appeared. The compound was found identical with the authentic sample of 5,6β-dihydroxy-5α-cholestane (LXXVII).

Characterization of the compound, m.p. 195° as 5-hydroxy-6β-acrylamido-5α-cholestane (LXXVIII)

The compound, m.p. 195° was analysed for $C_{30}H_{51}NO_2$. The I.R. spectrum showed bands at 3480 (OH), 3300 (NH), 1660 (amide-I), 1530 (amide-II) and 1630 cm^{-1} ($CH=CH_2$). In N.M.R. spectrum a singlet at δ 6.03 (disappeared on addition of D_2O) integrating for one proton was appeared and assigned to ($C_6-\underline{NH}-\overset{O}{\overset{\|}{C}}-$). A two protons doublet at δ 6.2 (J=4 Hz) assignable to $CH=C\underline{H}_2$, one proton triplet at δ 5.7 ascribable to ($C\underline{H}=CH_2$) and a multiplet at δ 4.21 for (C6-α$\underline{H}$, $W\frac{1}{2}$ = 10 Hz) were also present in N.M.R. spectrum. The 5α-hydroxy proton appeared as a broad singlet at δ 2.66. Methyl signals were observed at δ 1.08 (C10-$C\underline{H}_3$), 0.66 (C13-$C\underline{H}_3$), 0.91 and 0.83 (remaining methyl protons). The oxide ring was broken by acrylonitrile in such a manner that the nitrile group preferably attacks at secondary carbon rather than the tertiary carbon. The structure (LXXVIII) was further supported by its mass spectral study. The compound (LXXVIII) (Fig. 1) showed the molecular ion peak at m/z 457 ($C_{30}H_{51}NO_2$).

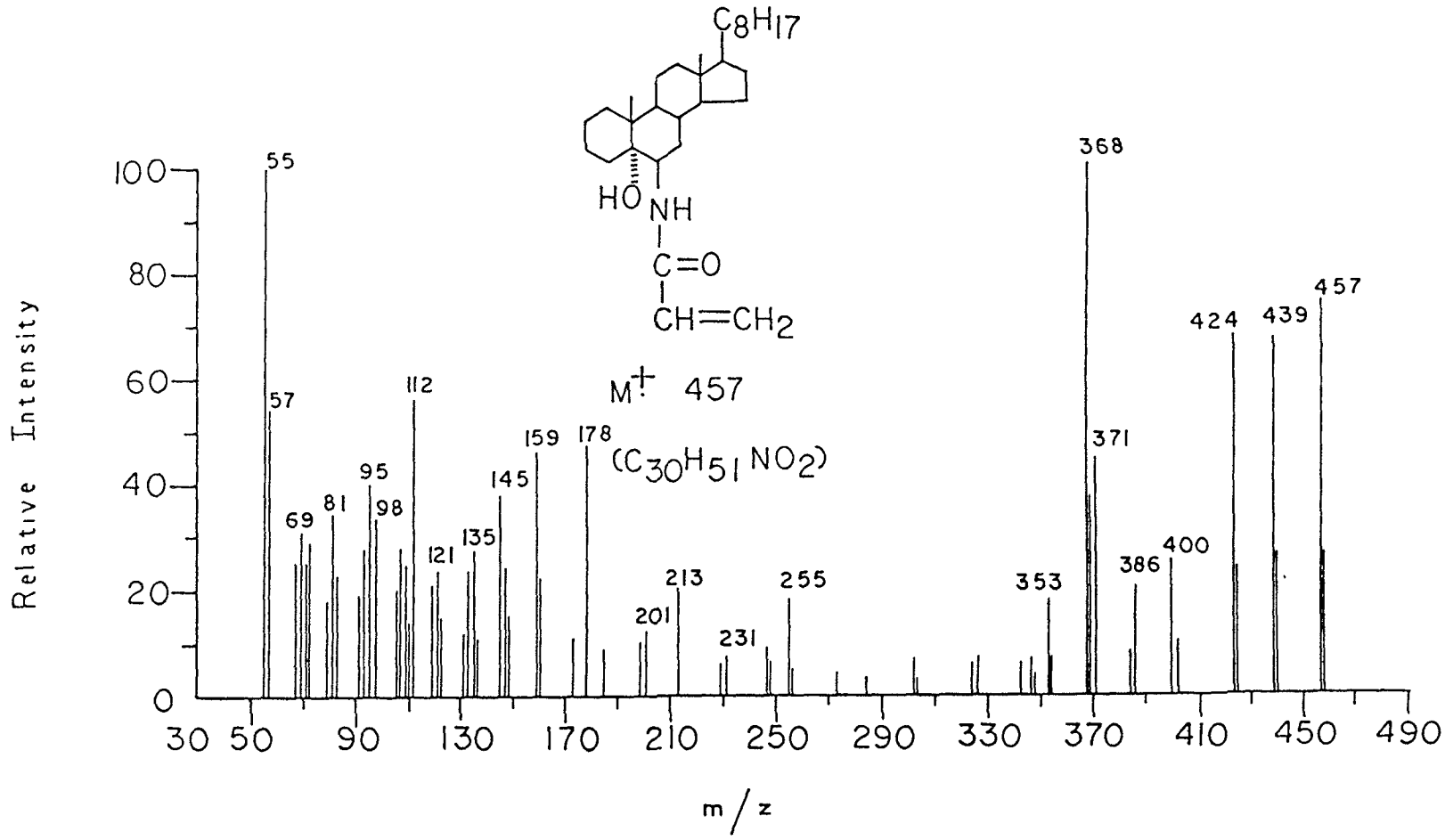
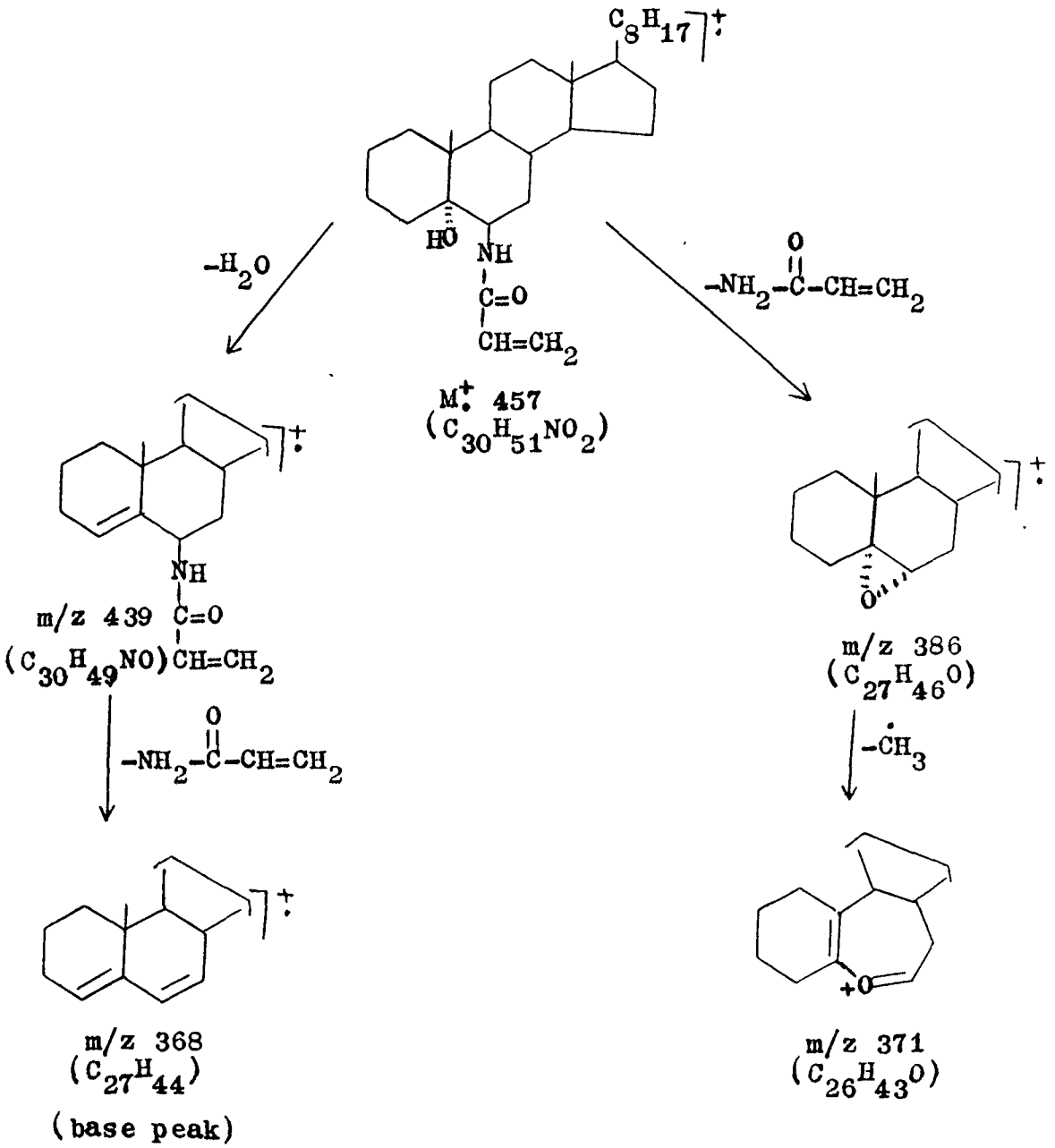


Fig. 1 Mass Spectrum of LXXVIII.

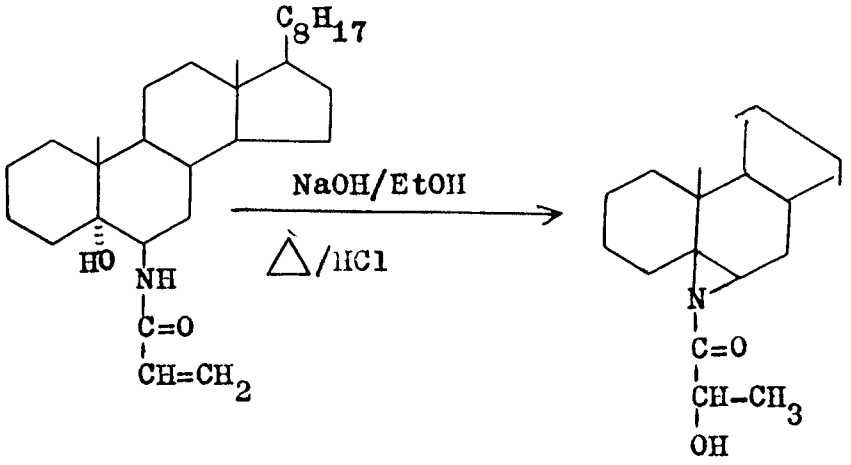
The other diagnostic peaks were at m/z 439 ($M^{+}\cdot - H_2O$), 424 (m/z 439-CH_3), 440 ($M^{+}\cdot$-OH), 425 (m/z 440-CH_3), 386 ($M^{+}\cdot - NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$), 371 (m/z 386-$CH_3$), 368 (m/z 439-$NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$; base peak), 255 (m/z 386-C_8H_{17}) and lower mass peaks. Scheme-1 explains the formation of some of the important ion peaks. which is tentative in nature.

Scheme - 1



Treatment of 5-hydroxy-6β-acrylamido-5α-cholestane (LXXVIII) with alcoholic sodium hydroxide

The compound (LXXVIII) was refluxed with alcoholic sodium hydroxide solution. The reaction mixture after usual work up provided a fine crystalline solid, m.p. 120°.



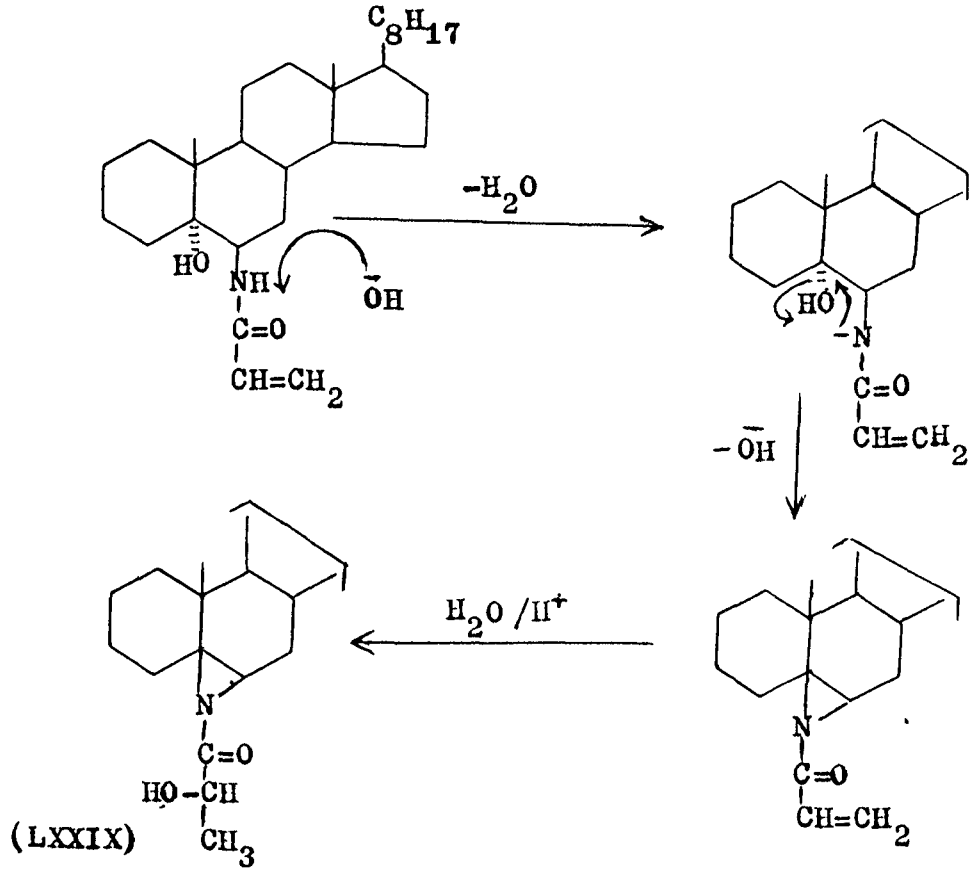
(LXXVIII) (LXXIX)

Characterization of the compound, m.p. 120° as N-(2'-hydroxy-2'-methyl)-acetyl-5β-cholestano [5,6-b] aziridine (LXXIX)

The compound, m.p. 120° showed the molecular composition $C_{30}H_{51}NO_2$. Bands observed in I.R. spectrum were at 1650 (tertiary amide) and 3400 cm^{-1} (OH). The band for double bond was not observed (negative tetranitromethane test). The N.M.R. spectrum showed a triplet at δ 2.36 for

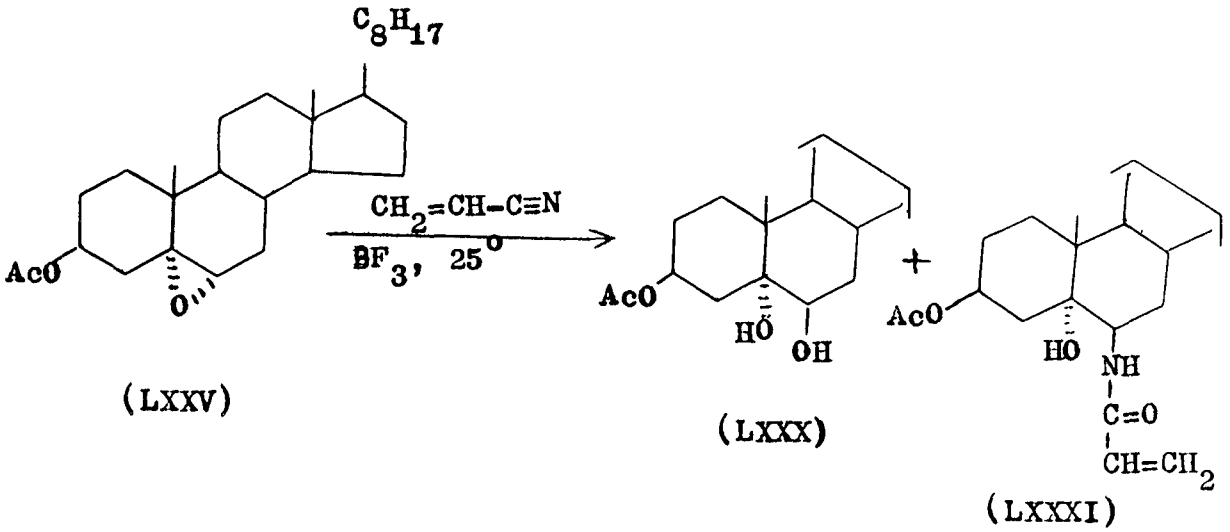
(C6-αH). A multiplet appeared at δ 3.60 integrating for one proton was assigned to ($-\underset{\underset{OH}{|}}{CH}-CH_3$) which indicated that the ethylene bond was saturated by the addition of water molecule in the presence of hydrochloric acid. A doublet of 2'-methyl protons was observed at δ 1.23. Hydroxy proton appeared as a singlet at δ 3.46 (disappeared on addition of D_2O). Mechanistically it was observed that the aziridine ring was β -oriented.[15] Methyl signals were seen at δ 1.03 (C10-CH_3), 0.68 (C13-CH_3), 0.98 and 0.83 (remaining methyl protons). On the basis of above elemental and spectral data the compound (LXXIX) was characterized as N-(2'-hydroxy, 2'-methyl)-5β-cholestano [5,6-b] aziridine. To account for the formation of (LXXIX) the following mechanism was proposed.

Scheme - 2



Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (LXXV) with acrylonitrile-borontrifluoride etherate

Boron trifluoride etherate was added to a stirred suspension of α-epoxide (LXXV) in acrylonitrile. After usual work up and column chromatography over silica gel, two solid compounds with m.p. 207° and 187° were obtained.



(LXXV) (LXXX) (LXXXI)

Characterization of the compound, m.p. 207° as 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (LXXX)

The compound, m.p. 207° (reported[17] m.p. 209°) was correctly analysed for $C_{29}H_{50}O_4$. The molecular composition showed the addition of one oxygen atom to the substrate. The I.R. spectrum exhibited absorption bands at 3400 (OH)

and 1730, 1240 ($CH_3-\overset{O}{\overset{\|}{C}}-O$). The compound (LXXX) was found identical with the authentic sample of 3β-acetoxy-5,6β-dihydroxy-5α-cholestane (LXXX).

Characterization of the compound, m.p. 187° as 3β-acetoxy-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXI)

The compound, m.p. 187° was analysed for $C_{32}H_{53}NO_4$. The I.R. spectrum exhibited bands at 3370 (OH), 3360 (NH), 1730 and 1240 ($CH_3-\overset{O}{\overset{\|}{C}}-O$), 1660 (amide-I), 1508 (amide II) and 1625 cm^{-1} ($CH=CH_2$). N.M.R. spectrum of the compound exhibited a broad multiplet at δ 5.11 ($W\frac{1}{2}$ = 18 Hz) integrating for one proton for C3α-H. The half band width showed that the A/B ring junction is trans.[18] A broad singlet at δ 5.9 (disappeared on addition of D_2O) integrating for one proton was assigned to (C6-NH-$\overset{O}{\overset{\|}{C}}$-) and a multiplet at δ 4.21 to (C6-αH; $W\frac{1}{2}$ = 10 Hz). The ethylenic protons were observed at δ 6.83 (J = 7 Hz)($CH=C\underline{H}_2$) and 5.61 ($C\underline{H}=CH_2$) as doublet and triplet respectively. A sharp singlet appeared at δ 1.95 for ($C\underline{H}_3-\overset{O}{\overset{\|}{C}}-O$). Methyl signals were seen from δ 0.66 to 1.16. On the basis of foregoing discussion the compound (LXXXI) was regarded as 3β-acetoxy-5-hydroxy-6β-acrylamido-5α-cholestane. The mass spectrum of (LXXXI) gave the molecular ion peak at m/z 515 followed by the significant

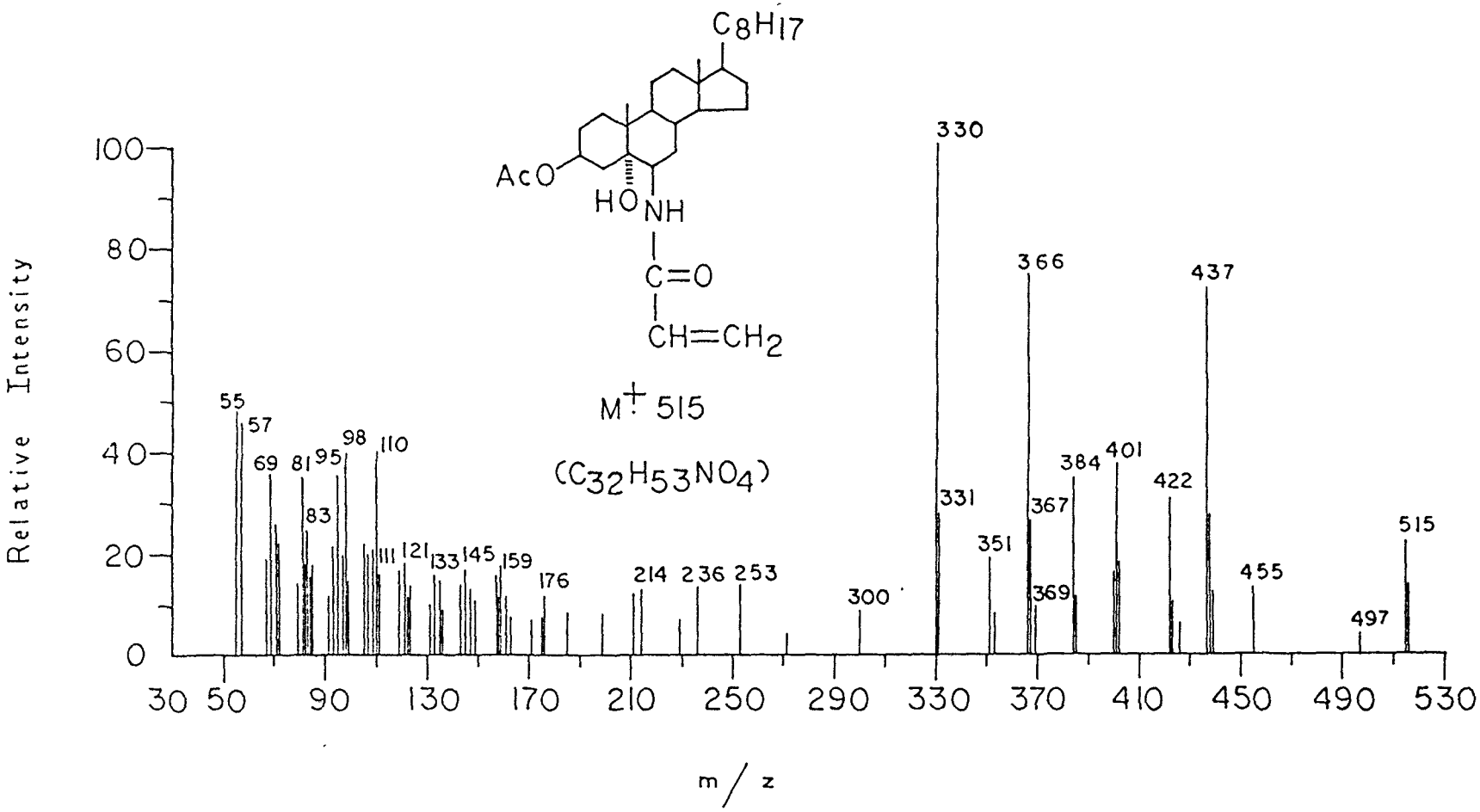
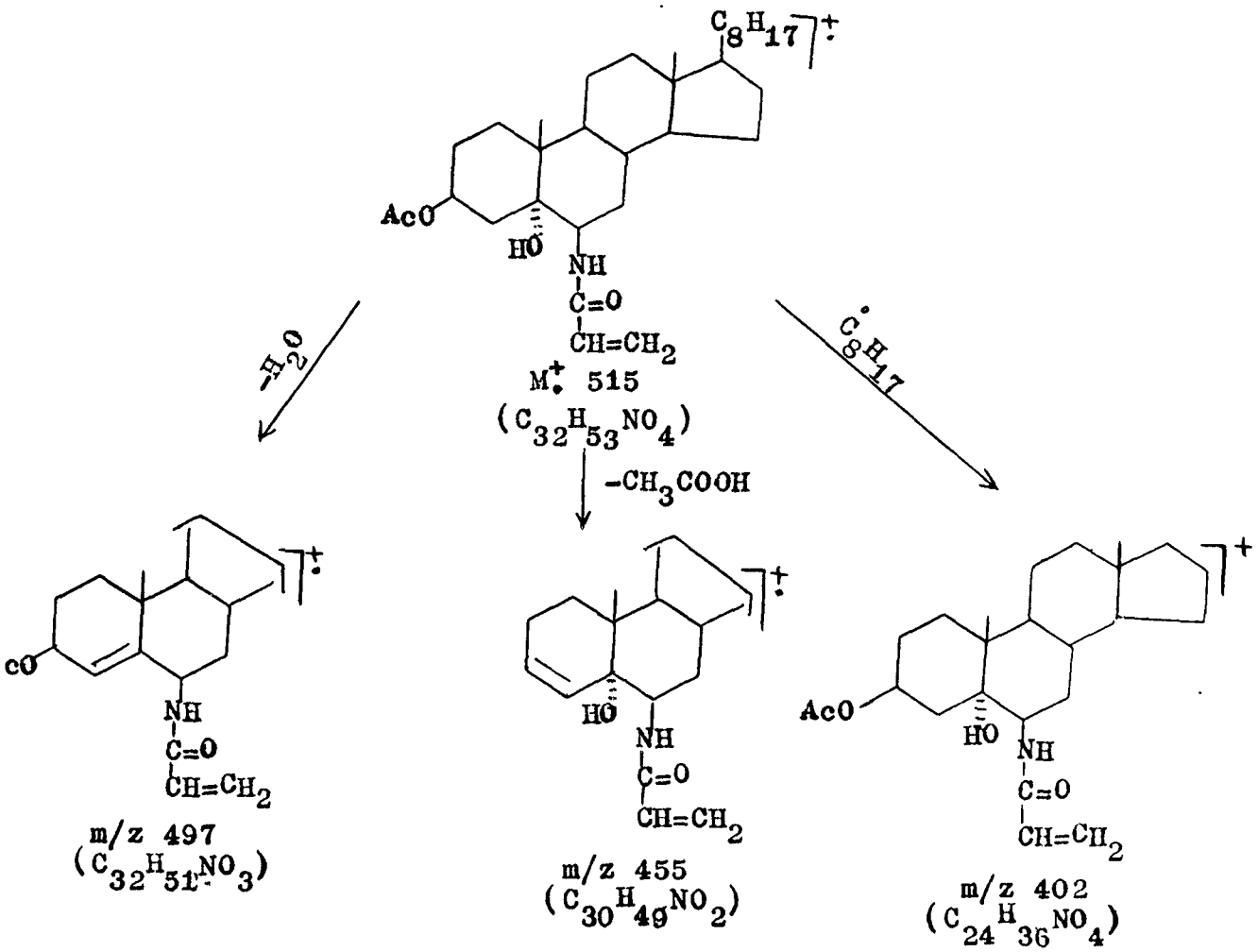


Fig. 2 Mass Spectrum of LXXXI.

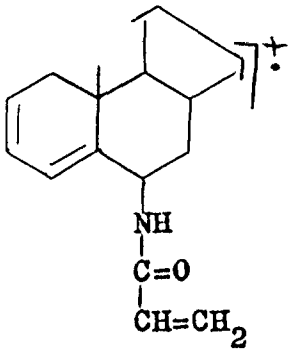
fragment ion peaks at m/z 497 ($M^+ - H_2O$), 437 (m/z 497-CH_3COOH), 455 ($M^+ - CH_3COOH$), 366 (m/z 437-$H_2N-\overset{O}{\overset{\|}{C}}-CH=CH_2$), 384 (m/z 455-$NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$), 369 (m/z 384-$CH_3$), 402 ($M^+ - C_8H_{17}$), 401 (m/z 402-H), 330 (m/z 401-$NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$; base peak), 331 (m/z 402-$NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$), 422 (m/z 437-$CH_3$), 351 (m/z 366-$CH_3$) and lower mass peaks. (Fig. 2, Scheme - 3).

Scheme - 3



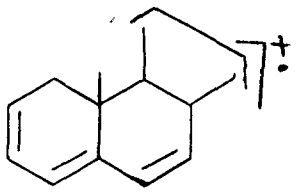
m/z 497
($C_{32}H_{51}NO_3$)

$-CH_3COOH$



m/z 437
($C_{30}H_{47}NO$)

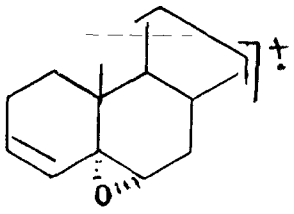
$-NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$



m/z 366
($C_{27}H_{42}$)

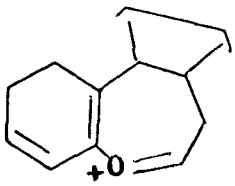
m/z 455
($C_{30}H_{49}NO_2$)

$-NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$



m/z 384
($C_{27}H_{44}O$)

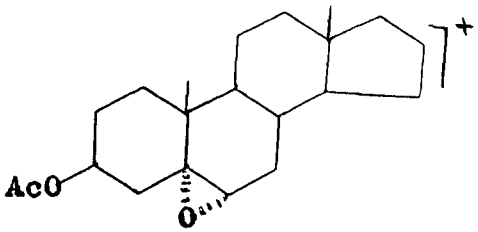
$-\dot{C}H_3$



m/z 369
($C_{26}H_{41}O$)

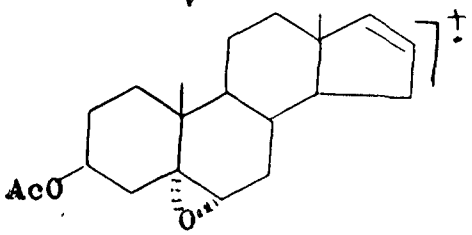
m/z 402
($C_{24}H_{36}NO_4$)

$-NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$



m/z 331
($C_{21}H_{31}O_3$)

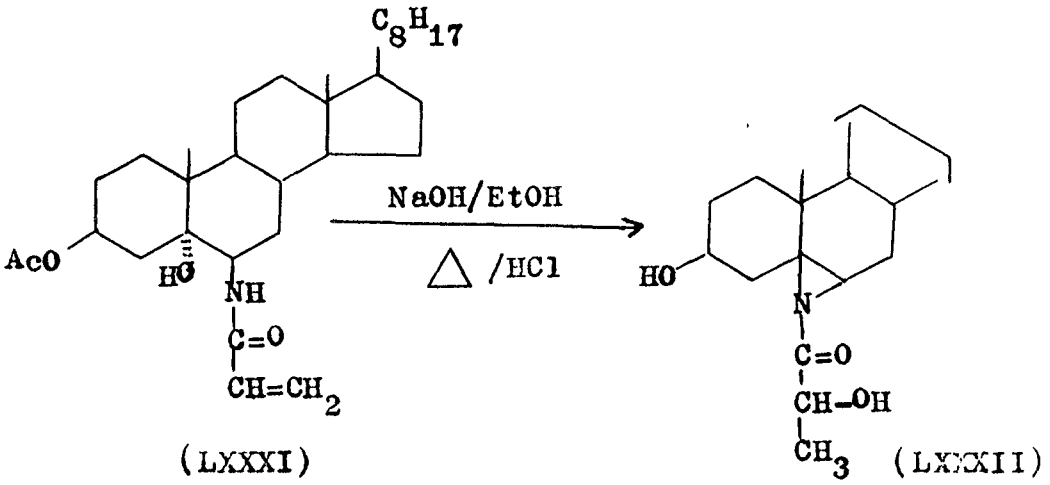
$-H^{\cdot}$



m/z 330
($C_{21}H_{30}O_3$)
(base peak)

Treatment of 3β-acetoxy-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXI) with alcoholic sodium hydroxide

The compound (LXXXI) was refluxed with alcoholic sodium hydroxide solution. After usual work up a crystalline solid, m.p. 158° was obtained.



(LXXXI) (LXXXII)

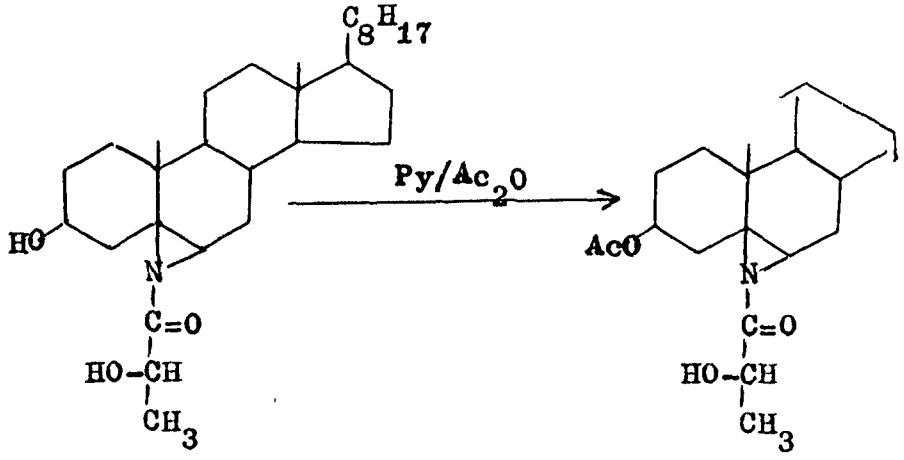
Characterization of the compound, m.p. 158° as N-(2'-hydroxy, 2'-methyl)-acetyl-3β-hydroxy-5β-cholestano [5,6-b] aziridine (LXXXII)

The compound, m.p. 158° was correctly analysed for $C_{30}H_{51}NO_3$. Bands were observed at 1650 cm^{-1} (tertiary amide) for aziridine and 3400 cm^{-1} (OH). The N.M.R. spectrum revealed a broad singlet at δ 3.66 integrating for one proton

ascribable to C3-$\alpha\underline{H}$ ($W\frac{1}{2}$ = 8 Hz). The half band width showed that the A/B ring junction is cis and C3-proton equatorially oriented.[18] On this basis aziridine ring was β -oriented. A triplet at δ 2.53 was assigned to C6-$\alpha\underline{H}$, and multiplet at δ 4.06 (1H) was observed for ($-\underset{OH}{\underline{C}H}-CH_3$) and a doublet at δ 1.15 for ($-\underset{OH}{C\underline{H}}-C\underline{H}_3$) was also present in N.M.R. spectrum. Hydroxy protons appeared together as singlet at δ 3.40 (disappeared on addition of D_2O). Methyl signals were seen at δ 1.08 (C10-$C\underline{H}_3$), 0.68 (C13-$C\underline{H}_3$), 0.90 and 0.82 (remaining methyl protons). On the basis of elemental analysis and spectral data the compound (LXXXII) was characterized as N-(2'-hydroxy-2'-methyl) acetyl-3β-hydroxy-5β-cholestano [5,6-b] aziridine.

Acetylation of compound (LXXXII) with acetic anhydride and pyridine

The compound (LXXXII) was treated with pyridine and acetic anhydride at room temperature. The reaction mixture after usual work up provided a crystalline compound, m.p. 147°.



(LXXXII) (LXXXIII)

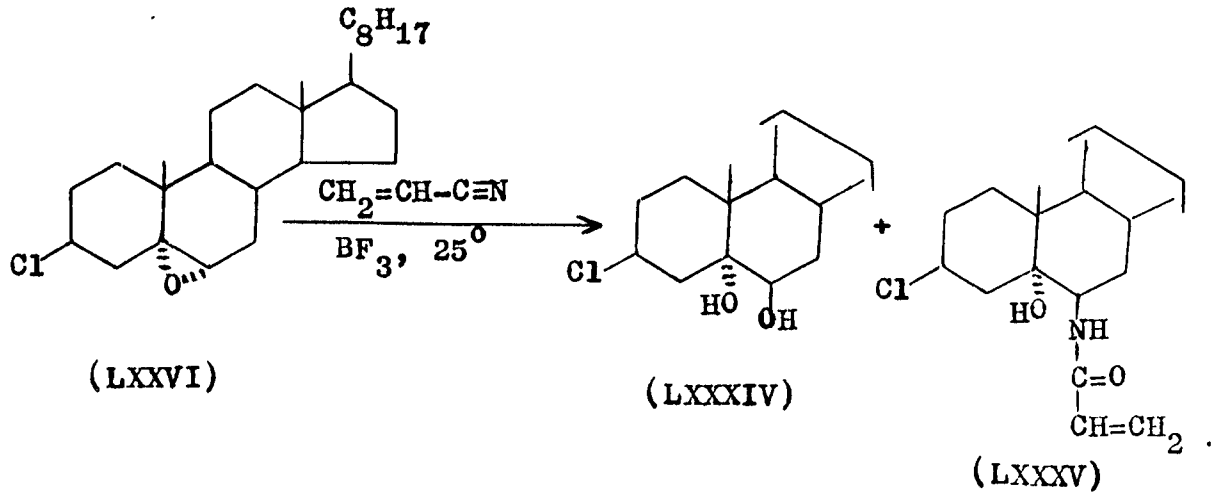
Characterization of the compound, m.p. 147° as N-(2'-hydroxy-2'-methyl) acetyl-3β-acetoxy-5β-cholestano[5,6-b] aziridine (LXXXIII)

The compound, m.p. 147° showed the molecular composition $C_{32}H_{53}NO_4$. Analysis showed the addition of two carbon atoms and one oxygen atom to the substrate (LXXXII) indicating that only one hydroxy group has been acetylated. The I.R. spectrum exhibited absorption bands at 3400 (OH), 1725, 1240 ($CH_3-\overset{O}{\overset{\|}{C}}-O$) and 1660 cm^{-1} (tertiary amide). The N.M.R. spectrum of the compound (LXXXIII) displayed a broad multiplet at δ 4.21 ($W\frac{1}{2}$ = 9 Hz) integrating for one proton was ascribable to C3-$\alpha\underline{H}$. The half band width showed that the ring junction was cis. A multiplet at δ 3.60 integrating for one proton was assigned to ($-\overset{OH}{\underset{|}{C}}\underline{H}-CH_3$) and a triplet at δ 2.45 to C6-$\alpha\underline{H}$.

The 2'-methyl protons gave a doublet at δ 1.25. 2'-Hydroxy proton appeared as singlet at 3.36 (disappeared on addition of D_2O). Methyl signal of acetate group was observed at δ1.96 and other methyl signals appeared at δ 1.19 (C10-$\underline{CH}_3$), 0.66 (C13-$\underline{CH}_3$), 0.9 and 0.81 (remaining methyl protons). On the basis of foregoing discussion the compound (LXXXIII) was regarded as N-(2'-hydroxy-2'-methyl)-acetyl-3β-acetoxy-5β-cholestano [5,6-b] aziridine.

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (LXXVI) with acrylonitrile-boron trifluoride etherate

Boron trifluoride etherate (as catalyst) was added dropwise over a period of 15 minutes to stirred suspension of 3β-chloro-5,6α-epoxy-5α-cholestane (LXXVI) in acrylonitrile at room temperature. After usual work up of the reaction mixture, residue obtained was chromatographed over silica gel. Two solid compounds having m.p. 123° and 177° were obtained.



(LXXVI) (LXXXIV) (LXXXV)

Characterization of the compound, m.p. 123° as 3β-chloro-5,6β-dihydroxy-5α-cholestane (LXXXIV)

The compound, m.p. 123° (reported m.p. 125-26°)[19] was correctly analysed for $C_{27}H_{47}O_2Cl$. The molecular composition showed the addition of one oxygen atom to the substrate (LXXVI). The I.R. spectrum exhibited absorption bands at 3450 (OH) and 760 cm^{-1} (C-Cl). The compound was found identical with authentic sample of 3β-chloro-5,6β-dihydroxy-5α-cholestane (LXXXIV).

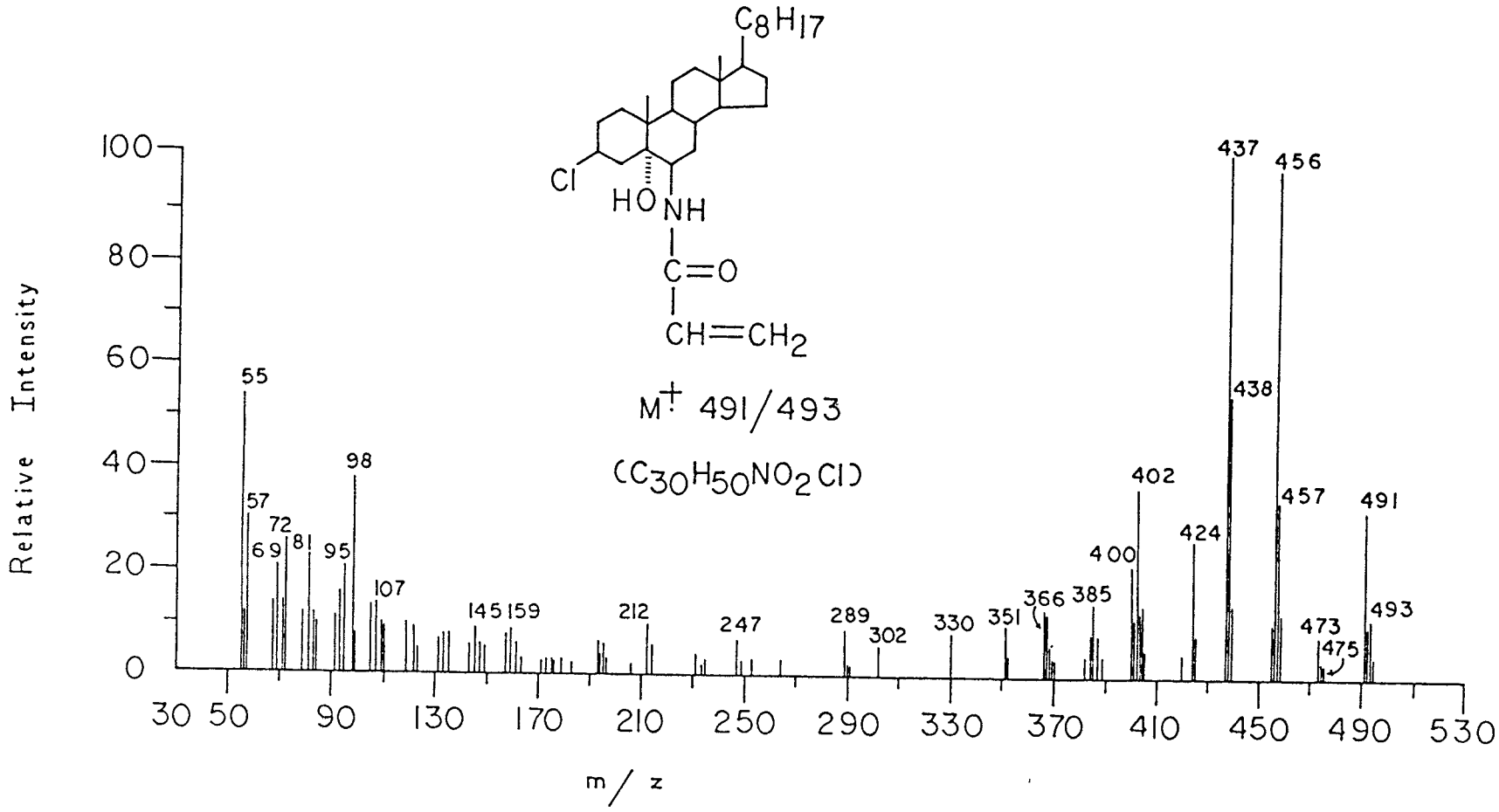
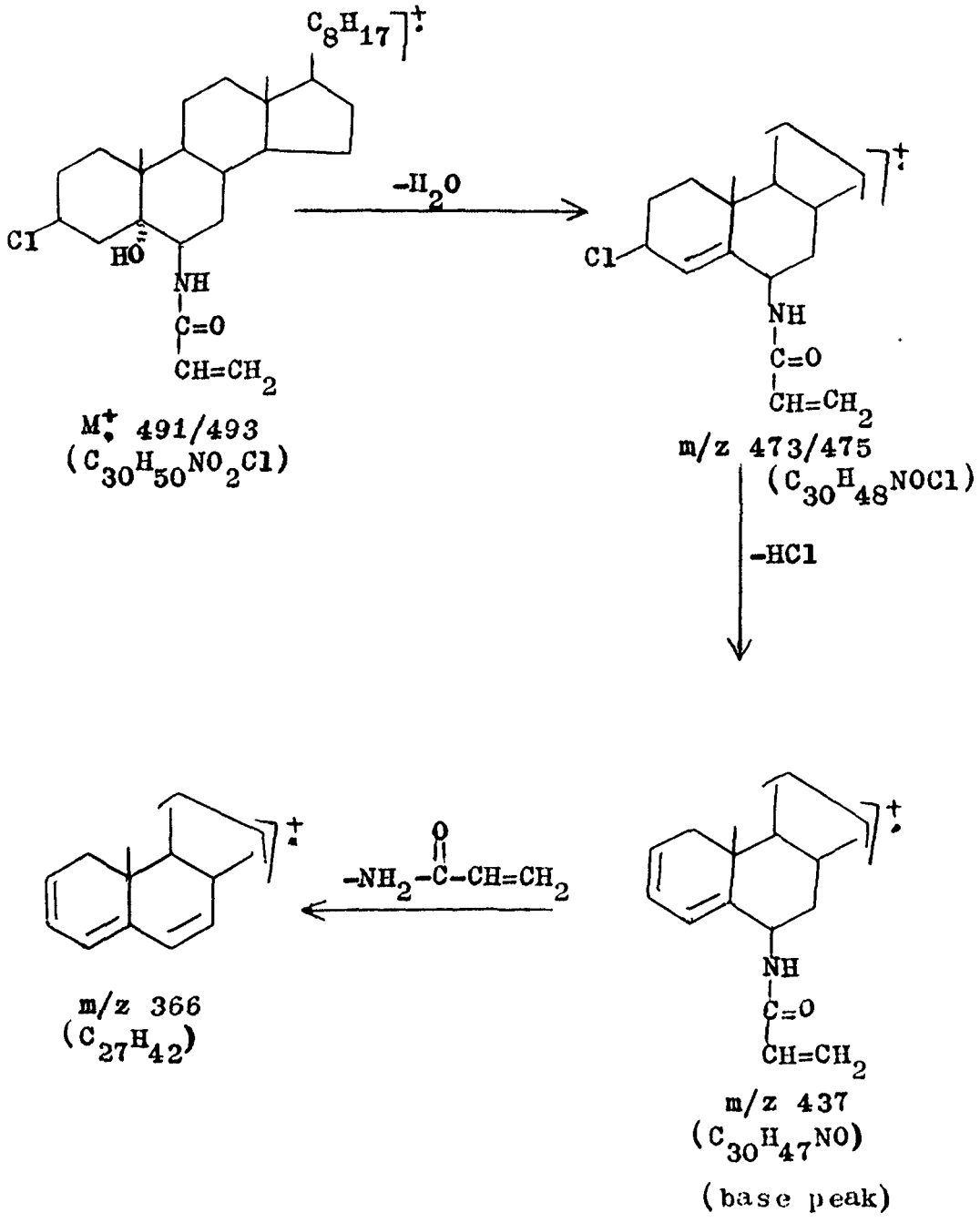


Fig. 3 Mass Spectrum of LXXXV.

Characterization of the compound, m.p. 177° as 3β-chloro-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXV)

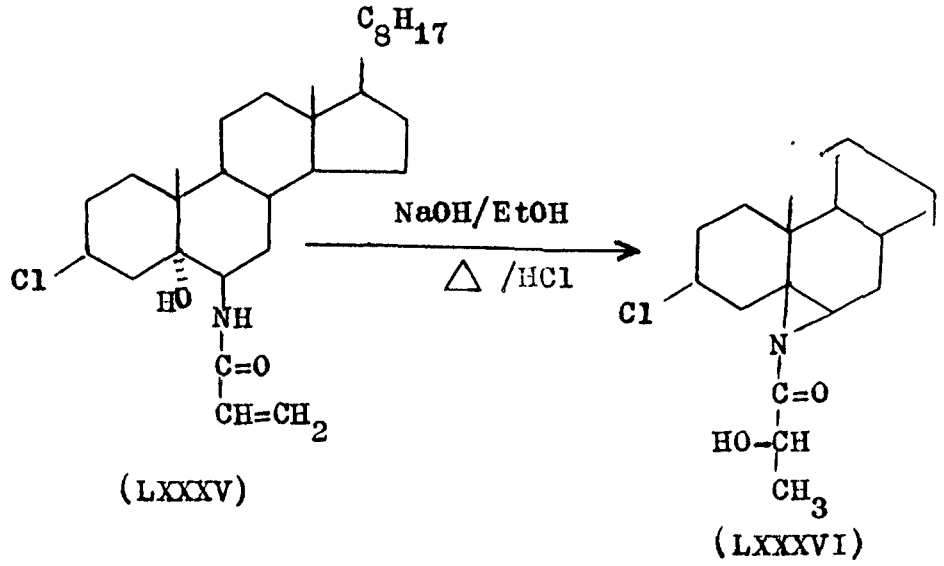
The compound, m.p. 177° was analysed for $C_{30}H_{50}NO_2Cl$. The I.R. spectrum showed bands at 3450 (OH, NH), 1665 (amide I), 1530 (amide II), 1630 ($-CH=CH_2$) and 760 cm^{-1} (C-Cl). In N.M.R. spectrum a multiplet was revealed at δ 4.4 ($W\frac{1}{2}$ = 17 Hz) integrating for two protons (C3-$\alpha\underline{H}$ and C6-$\alpha\underline{H}$). A singlet at δ 6.60 (disappeared on addition of D_2O) integrating for one proton was assigned to ($-C6-N\underline{H}-\overset{O}{\overset{\|}{C}}$) and a triplet at δ 5.8 to ($-C\underline{H}=CH_2$). A doublet appeared at δ 6.2 (J=4 Hz) which was ascribed to ($CH=C\underline{H}_2$). The C5-hydroxy proton was appeared as broad singlet at δ 3.73 (disappeared on addition of D_2O). Methyl signals were obtained at δ 1.16 ($C10-C\underline{H}_3$), 0.70 ($C13-C\underline{H}_3$), 0.90 and 0.83 (remaining methyl protons). The compound (LXXXV) (Fig. 3) showed the molecular ion peaks at m/z 491/493 (3:1) along with significant peaks at m/z 473/475 (m/z 491/493-H_2O; 3:1), 437 (m/z 473/475-HCl), 456 (M-Cl), 455 (m/z 456-H), 422 (m/z 437-CH_3), 366 (m/z 437-$NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$), 466 (m/z 437-$NH_2-\overset{O}{\overset{\|}{C}}-CH=CH_2$), 351 (m/z 366-$CH_3$) and lower mass peaks. The formation of some fragment ions are given in Scheme-4.

Scheme - 4


C_8H_{17}
Cl
HO
NH
C=O
CH=CH$_2$
M^+ 491/493
($C_{30}H_{50}NO_2Cl$)
$-H_2O$
Cl
NH
C=O
CH=CH$_2$
m/z 473/475
($C_{30}H_{48}NOCl$)
-HCl
NH
C=O
CH=CH$_2$
m/z 437
($C_{30}H_{47}NO$)
(base peak)
$-NH_2-C(=O)-CH=CH_2$
m/z 366
($C_{27}H_{42}$)

Treatment of 3β-chloro-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXV) with alcoholic sodium hydroxide

The compound (LXXXV) was refluxed with alcoholic sodium hydroxide solution. The reaction mixture after usual work up provided a fine crystalline solid, m.p. 212.



(LXXXV) (LXXXVI)

Characterization of the compound, m.p. 212° as N-(2'-hydroxy-2'-methyl)-acetyl-3β-chloro-5β-cholestano [5,6-b] aziridine (LXXXVI)

The compound, m.p. 212° showed the molecular composition $C_{30}H_{50}NO_2Cl$. The bands were observed in I.R. spectrum at 3400 (OH), 1660 (tertiary amide) and 765 cm^{-1} (C-Cl). N.M.R. spectrum exhibited a broad multiplet at δ 4.20 ($W\frac{1}{2}$ = 6 Hz)

integrating for one proton and was assigned to C3-$\alpha\underline{H}$. The half band width showed C3-proton equatorial and aziridine ring was β -oriented. C6-proton appeared at δ 2.34 as triplet and ($\underline{CH}(OH)-CH_3$) was observed at δ 3.5 as multiplet. 2'-Methyl protons appeared as doublet at δ 1.20, hydroxy proton appeared as broad singlet at δ 3.40 (disappeared on addition of D_2O). Methyl signals were seen at δ 1.01 (C10-$C\underline{H}_3$), 0.66 (C13-$C\underline{H}_3$), 0.90 and 0.80 (remaining methyl protons).

Experimental

All melting points were observed on a Kofler apparatus and are uncorrected. Infrared spectra (I.R.) were determined with a Perkin-Elmer 237 spectrophotometer in Nujol. I.R. values are given in cm^{-1}. Nuclear Magnetic Resonance (N.M.R.) were run in $CDCl_3$ on a Varian A-60 instrument with tetramethyl silane (T.M.S.) as the internal standard. The N.M.R. values are given in ppm (δ). Mass spectra were recorded on JMSD-300 mass spectrometer at 70 eV. Thin layer chromatographic (TLC) plates were coated with silica gel G and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60-80°. Anhydrous sodium sulphate (Na_2SO_4) was used as the drying agent. The abbreviations "s, d, t, m and d d" denote "singlet, doublet, triplet, multiplet and double doublet respectively.

5,6α-Epoxy-5α-cholestane (LXXIV)

Cholest-5-ene (6 g) in chloroform (40 ml) was treated with a solution of perbenzoic acid (1.1 mole equivalent) in chloroform and left at -8° for 20 hrs. The mixture was then washed with ice-cold sodium bicarbonate solution (5%), water

and sodium thiosulphate solution. Evaporation of the solvent yielded (LXXIV) as an oil which was crystallized from acetone as needles (4.3 g) m.p. 76° (reported[17] m.p. 76°).

Reaction of 5,6α-epoxy-5α-cholestane (LXXIV) with acrylonitrile-BF_3-etherate: 5,6β-Dihydroxy-5α-cholestane (LXXVII) and 5-hydroxy-6β-acrylamido-5α-cholestane (LXXVIII)

Borontrifluoride-etherate (2 ml) was added dropwise over 15 min. to a stirred suspension of α-epoxide (LXXIV) (2.0 g) in acrylonitrile (20 ml) at room temperature. The resulting solution was further stirred for 25 minutes and then diluted with water and extracted with ether. The organic layer was washed with sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was chromatographed over silica gel (40 g). Elution with light petroleum: ether (10:1) gave the diol (LXXVII), recrystallized from light petroleum (0.40 g), m.p. 124° (reported[16] m.p. 125.5).

Further elution with light petroleum: ether (8:1) furnished (LXXVIII), recrystallized from light petroleum (1.3 g), m.p. 195° (Found: C, 78.77; H, 11.10; N, 3.10. $C_{30}H_{51}NO_2$ requires: C, 78.77; H, 11.15; N, 3.06%).

I.R. : νmax. 3480 (OH), 3300 (NH), 1660 (amide-I), 1530 (amide-II) and 1630 cm^{-1} ($CH=CH_2$).

N.M.R.: δ 6.03 s (C6-N<u>H</u>-C(=O)-), 6.2d (CH=C<u>H</u>$_2$; J=3 Hz), 5.7t (C<u>H</u>=CH$_2$), 4.21m (C6-α<u>H</u>, $W\frac{1}{2}$ = 10 Hz), 2.66br,s (OH), 1.08 (C10-C<u>H</u>$_3$), 0.66 (C13-C<u>H</u>$_3$), 0.91 and 0.83 (remaining methyl protons).

Mass : M^+ 457.

<u>Treatment of 5-hydroxy-6β-acrylamido-5α-cholestane (LXXVIII) with alcoholic sodium hydroxide:N-(2'-hydroxy,2'-methyl)-acetyl-5β-cholestano [5,6-b] aziridine (LXXIX)</u>

The compound (LXXVIII) (1.0 g) was dissolved in ethanol and to this was added an alcoholic sodium hydroxide solution (10%, 20 ml). The reaction mixture was refluxed for 3 hrs and then acidified with HCl, and extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulphate. The oil thus obtained on evaporation of the solvent gave the compound (LXXIX) (0.6 g) m.p. 120°C on crystallization from ethanol. (Found: C, 78.76; H, 11.12; N, 3.04. $C_{30}H_{51}NO_2$ requires: C, 78.77; H, 11.6; N, 3.06%).

I.R. : ν max. 3400 (OH), 1650 cm^{-1} (tertiary amide).

N.M.R.: δ 2.36t (C6-α<u>H</u>), 3.60m (-C<u>H</u>(OH)-CH$_3$), 1.23d (-CH(OH)-C<u>H</u>$_3$), 3.46s (O<u>H</u>), 1.03 (C10-C<u>H</u>$_3$), 0.68 (C13-C<u>H</u>$_3$), 0.98 and 0.83 (remaining methyl protons).

3β-Acetoxy-5,6α-epoxy-5α-cholestane (LXXV)

Cholesteryl acetate (10 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equivalent) in chloroform and left at -8° for 20 hrs. The mixture was then washed with ice-cold sodium bicarbonate solution. Evaporation of the solvent gave (LXXV) as an oil. The oil was chromatographed over silica gel. Elution with light petroleum-ether (10:1) gave a compound which was crystallized from acetone as needles (8.0 g) m.p. 97° (reported[17] m.p. 97°).

Reaction of 3β-acetoxy-5,6α-epoxy-5α-cholestane (LXXV) with acrylonitrile-BF_3-etherate: 3β-Acetoxy-5,6-dihydroxy-5α-cholestane (LXXX) and 3β-acetoxy-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXI)

α-Epoxide (LXXV) (2.0 g) was treated with acrylonitrile (20 ml) and BF_3-etherate (2 ml) at room temperature for 25 minutes. The reaction mixture was worked up as described for (LXXIV). The residue obtained after the removal of the solvent was chromatographed over silica gel (40 g). Elution with light petroleum ether: ether(10:1) afforded the diol (LXXVII) (0.6 g), m.p. 207° (reported[17], m.p. 209°).

Further elution with light petroleum ether: ether (5:1) gave (LXXVIII) which was recrystallized from ethanol (1.4 g)

m.p. 187° (Found: C, 74.30; H, 10.30; N, 2.68. $C_{32}H_{53}NO_4$ requires: C, 74.56; H, 10.29; N, 2.71%).

I.R. ν max. 3370 (OH), 3360 (NH), 1730, 1240 ($CH_3-\overset{O}{\overset{\|}{C}}-O$), 1660 (amide I), 1508 (amide II , 1625 cm^{-1} ($CH=CH_2$).

N.M.R.: δ 6.83 d ($CH=C\underline{H}_2$; J=7 Hz), 5.9 br,s ($N\underline{H}$), 5.61t ($C\underline{H}=CH_2$), 5.11 m (C3-$\alpha\underline{H}$; $W\frac{1}{2}$ = 18 Hz), 4.21 m (C6-$\alpha\underline{H}$; $W\frac{1}{2}$ = 10 Hz), 1.95 ($C\underline{H}_3-\overset{O}{\overset{\|}{C}}-O$), 3.91 br,s (OH), 1.13 (C10-$C\underline{H}_3$), 0.66 (C13-$C\underline{H}_3$), 0.91 and 0.81 (remaining methyl protons).

Mass : M^+ 515.

Treatment of 3β-acetoxy-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXI) with alcoholic sodium hydroxide: N-(2'-hydroxy,2'-methyl)-acetyl-3β-hydroxy-5β-cholestano [5,6-b] aziridine (LXXXII)

The compound (LXXXI) (1.0 g) dissolved in ethanol was mixed with alcoholic sodium hydroxide (10%; 20 ml). The reaction mixture was refluxed for 3 hrs. then it was acidified with hydrochloric acid and extracted with ether. The ethereal layer was washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate anhydrous. On evaporation of the solvent the compound (LXXXII) (0.60 g) was obtained m.p. 158° (Found: C, 76.90; H, 10.70; N, 3.69. $C_{30}H_{51}NO_3$ requires: C, 76.11; H, 10.71; N, 3.71%).

I.R. : ν max. 3400 (OH), 1650 cm^{-1} (tertiary amide).

N.M.R.: δ 3.66 br,s (C3-$\underline{H}$; $W\frac{1}{2}$ = 8 Hz), 4.06 m ($-\underset{OH}{\underset{|}{C}}\underline{H}-\underset{CH_3}{\underset{|}{C}}H$), 3.40s ($O\underline{H}$), 2.53t (C6-$\underline{H}$), 1.15d ($-CH-C\underline{H}_3$), 1.08 ($C10-C\underline{H}_3$), 0.68 ($C13-C\underline{H}_3$), 0.90 and 0.82 (remaining methyl protons).

Acetylation of (LXXXII)

A mixture of N-(2'-hydroxy,2'-methyl)-acetyl-3β-hydroxy-5β-cholestano [5,6-b] aziridine (LXXXII) (100 mg), purified pyridine (0.6 ml) and freshly distilled acetic anhydride (0.4 ml) was allowed to stand at room temperature for 48 hrs. The reaction mixture was poured into water and precipitate thus obtained was extracted with ether. The ethereal layer was washed with water, dilute hydrochloric acid (until free from pyridine), water, sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent provided (LXXXIII) (75 mg) recrystallized from methanol m.p. 147° (Found: C, 74.51; H, 10.27; N, 2.69. $C_{32}H_{53}NO_4$ requires C, 74.56; H, 10.29; N, 2.71%).

I.R. : ν max. 1725, 1240 ($CH_3-\overset{O}{\overset{\|}{C}}-O$), 3400 (OH), 1660 cm^{-1} (tertiary amide).

N.M.R.: δ 4.21 br,m (C3-αH, $W\frac{1}{2}$ ≈ 9 Hz), 3.60m ($-\underset{\underset{O}{\|}}{\overset{CH_3}{\overset{|}{C}}}H-OH$), 3.36s (OH), 2.45t (-C6-αH), 1.96s ($CH_3-\underset{\underset{O}{\|}}{C}-O$), 1.21d ($-\underset{OH}{\overset{|}{C}}H-CH_3$), 1.19 (C10-$CH_3$), 0.66 (C13-$CH_3$), 0.91 and 0.81 (remaining methyl protons).

3β-Chloro-5,6α-epoxy-5α-cholestane (LXXVI)

Cholesteryl chloride (11 g) in chloroform (100 ml) was treated with a solution of perbenzoic acid (1.1 mole equivalent) in chloroform and left at -8° for 20 hrs. The mixture was then washed with ice-cold sodium bicarbonate solution (5%), water and sodium thiosulphate solution. Evaporation of the solvent yielded (LXXVI) as an oil which was crystallized from acetone as needles (8.1 g), m.p. 89° (reported[19] m.p. 89.5-90.5°).

Reaction of 3β-chloro-5,6α-epoxy-5α-cholestane (LXXVI) with acrylonitrile-BF_3-etherate: 3β-Chloro-5,6β-dihydroxy-5α-cholestane (LXXXIV) and 3β-chloro-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXVI)

To a stirred suspension of 3β-chloro-5,6α-epoxy-5α-cholestane (LXXVI) (2.0 g) in acrylonitrile (20 ml) at room temperature borontrifluoride-etherate (2 ml) was added dropwise over 15 minutes. The resulting solution was further

stirred for 25 minutes and then diluted with water and extracted with ether. The organic layer was washed with sodium bicarbonate solution (5%), water and dried over anhydrous sodium sulphate. Removal of the solvent provided an oil which was chromatographed over silica gel (40 g). Elution with petroleum ether: ether (15:1) gave the diol (LXXXIV) which was recrystallized from methanol (0.6 g), m.p. 123° (reported[19], m.p. 126°).

Further elution with petroleum ether: ether (9:1) gave (LXXXVI) which was recrystallized from ethyl alcohol (1.35 g) m.p. 177° (Found: C, 73.12; H, 10.14; N, 2.80; $C_{30}H_{50}NO_2Cl$ requires: C, 73.24; H, 10.17; N, 2.84%).

I.R. : ν max. 3450 (OH, NH), 1665 (amide-I), 1530 (amide-II), 1630 ($CH=CH_2$), 760 cm^{-1} (C-Cl).

N.M.R.: δ 6.21d ($CH=C\underline{H}_2$; J=4 Hz), 6.06br,s ($N\underline{H}$), 4.4m (C3-$\alpha\underline{H}$; $W\frac{1}{2}$ = 17 Hz), 4.1m (C6-$\alpha\underline{H}$), 3.37br,s ($O\underline{H}$), 5.8t($C\underline{H}=CH_2$), 1.16 (C10-$C\underline{H}_3$), 0.70 (C13-$C\underline{H}_3$), 0.90 and 0.83 (remaining methyl protons).

Mass: 491/493

Treatment of 3β-chloro-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXV) with alcoholic sodium hydroxide: N-(2'-hydroxy,2'-methyl)-acetyl-3β-chloro-5β-cholestano [5,6-b] aziridine (LXXXVI)

The compound (LXXXV) (1.0 g) was treated with alcoholic sodium hydroxide solution (10%; 20 ml) the reaction mixture was refluxed for 3 hrs. then it was acidified with hydrochloric acid and extracted with ether. Ethereal layer was washed with water, sodium bicarbonate solution (5%), water and dried over sodium sulphate anhydrous. On evaporation of the solvent, the compound (LXXXVI) was obtained which was recrystallized from ethanol (0.6 g); m.p. 212° (Found: C, 73.20; H, 10.15; N, 2.83. $C_{30}H_{50}NO_2Cl$ requires: C, 73.24; H, 10.17; N, 2.84%).

I.R. : ν max. 3400 (OH), 1660 (tertiary amide), 765 cm^{-1} (C-Cl).

N.M.R.: δ 4.20 br,m (C3-αH; $W\frac{1}{2}$ = 6 Hz), 3.5m ($-\underset{OH}{\underset{|}{C}}\underline{H}-\underset{CH_3}{\underset{|}{C}}-OH$), 3.40s (OH), 2.34t (C6-αH), 1.20d ($-CH-CH_3$), 1.01 (C10-CH_3), 0.66 (C13-CH_3), 0.90 and 0.80 (remaining methyl protons).

The mass spectra were measured in a JMSD-300 mass spectrometer at 70 eV using a direct insertion technique at a source temperature of about 250°C.

The value (m/z) of the fragment ions from various compounds are tabulated below. The value in parentheses are the relative abundance (%) of the peaks with respect to base peak as 100%.

5-Hydroxy-6β-acrylamido-5α-cholestane (LXXVIII)

$M^{+\cdot}$ 457 (74.00; $C_{30}H_{51}NO_2$), m/z 438 (31.00), 439 (67.00), 425 (23.00), 424 (68.00), 402 (10.00), 400 (25.00), 386 (20.00), 384 (8.00), 371 (44.00), 369 (37.00), 368 (100), 354 (7.00), 353 (17.00), 348 (4.00), 346 (7.00), 342 (6.00), 326 (7.00), 324 (6.00), 303 (3.00), 302 (7.00), 284 (3.00), 273 (4.00), 256 (5.00), 255 (18.00), 248 (6.00), 247 (9.00), 231 (7.00), 229 (6.00), 213 (20.00), 201 (12.00), 199 (10.00), 185 (9.00), 179 (8.00), 178 (47.00), 173 (11.00), 161 (30.00), 160 (22.00), 159 (46.00), 149 (15.00), 147 (24.00), 145 (37.00), 136 (11.00), 135 (27.00), 133 (23.00), 131 (12.00), 123 (15.00), 121 (24.00), 119 (21.00), 112 (56.00), 110 (14.00), 109 (25.00), 107 (28.00),

105 (20.00), 98 (34.00), 95 (40.00), 93 (27.00), 91 (19.00), 83 (23.00), 81 (34.00), 79 (18.00), 72 (29.00), 71 (25.00), 69 (30.00), 67 (25.00), 57 (54.00), 55 (99.00).

3β-Acetoxy-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXI)

$M^{+\cdot}$ 515 (22.00; $C_{32}H_{53}NO_4$), m/z 497 (4.00), 456 (10.00), 455 (13.00), 439 (12.00), 438 (27.00), 437 (71.00), 426 (6.00), 423 (10.00), 422 (30.00), 402 (18.00), 401 (37.00), 400 (16.00), 385 (11.00), 384 (34.00), 367 (26.00), 366 (74.00), 353 (8.00), 351 (19.00), 331 (28.00), 330 (100), 300 (8.00), 271 (4.00), 253 (14.00), 236 (13.00), 229 (7.00), 214 (13.00), 211 (12.00), 199 (8.00), 185 (8.00), 176 (11.00), 175 (7.00), 171 (6.00), 163 (8.00), 161 (11.00), 159 (17.50), 158 (12.00), 157 (16.00), 149 (11.00), 147 (13.00), 145 (17.00), 143 (13.00), 136 (4.00), 135 (15.00), 133 (16.00), 131 (10.00), 123 (14.00), 120 (12.00), 121 (18.00), 119 (17.00), 111 (16.00), 110 (40.00), 109 (21.00), 107 (20.00), 105 (22.00), 99 (15.00), 98 (40.00), 97 (20.00), 95 (36.00), 93 (22.00), 91 (12.00), 85 (18.00), 84 (16.00), 83 (25.00), 82 (18.00), 81 (35.00), 72 (22.00), 71 (36.00), 69 (36.00), 67 (19.00), 57 (46.00), 55 (48.00).

3β-Chloro-5-hydroxy-6β-acrylamido-5α-cholestane (LXXXV)

M^+ 491 (32.00)/493 (11.00) ($C_{30}H_{50}NO_2Cl$), m/z 475 (3.00), 473 (8.00), 457 (34.00), 456 (97.00), 439 (14.00), 438 (54.00), 437 (100), 425 (8.00), 424 (26.00), 420 (4.00), 405 (4.00), 404 (14.00), 403 (12.00), 402 (36.00), 401 (11.00), 400 (21.00), 389 (4.00), 387 (8.00), 385 (14.00), 384 (8.00), 382 (4.00), 370 (3.00), 369 (3.50), 368 (6.00), 367 (12.00), 366 (13.00), 352 (4.00), 351 (10.00), 330 (8.00), 302 (6.00), 289 (9.00), 264 (3.00), 247 (7.00), 214 (6.00), 212 (10.00), 195 (6.00), 193 (6.50), 161 (6.00), 159 (9.00), 157 (8.00), 149 (5.00), 147 (6.00), 145 (9.00), 143 (6.00), 135 (8.00), 133 (8.00), 131 (7.00), 123 (5.00), 121 (9.00), 119 (9.50), 110 (9.00), 109 (10.00), 107 (14.00), 105 (13.00), 99 (8.00), 98 (38.00), 95 (21.00), 93 (16.00), 91 (11.00), 84 (10.00), 83 (12.00), 81 (22.50), 78 (12.00), 72 (26.00), 69 (21.00), 67 (14.00), 57 (30.00), 55 (54.00).

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Synthesis of Steroidal Oxathiolanes

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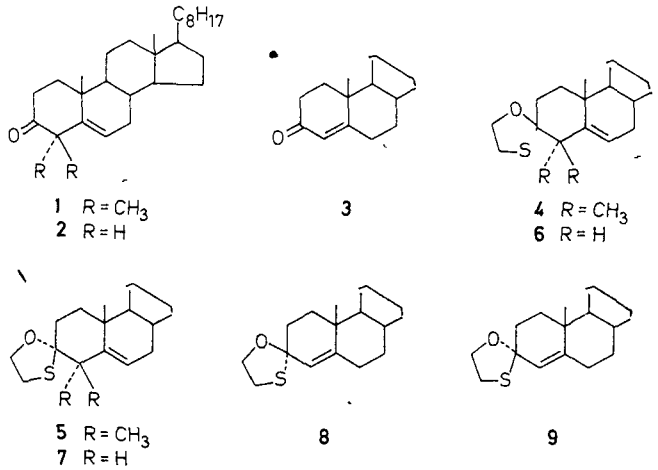
Synthese von Steroid-Oxathiolanen

A number of papers related to the synthesis of steroidal oxathiolanes have been reported [1–4]. This paper is concerned with the synthesis of isomeric oxathiolanes from sterically hindered 4,4-dimethylcholest-5-en-3-one **1**, cholest-5-en-3-one **2** and cholest-4-en-3-one **3**.



Ketone **1** on treatment with β-mercaptoethanol in dry benzene using p-toluenesulphonic acid as catalyst yielded compounds melting at 130°C, **4** and 140°C, **5**. The compounds m.p. 130°C and 140°C were correctly analysed for $C_{31}H_{52}OS$. The molecular composition shows that they are isomeric. I.r. spectrum of the compound m.p. 130°C exhibited a characteristic band at 1045 cm^{-1} and compound m.p. 140°C showed band at 1060 cm^{-1} for hemithioketal ring [1]. The distinction between **4** and **5** may be explained with the help of n.m.r. spectroscopy. N.m.r. spectrum of **4** revealed a distorted triplet for two protons at δ 4.2 (OCH_2), a clear triplet integrating for two protons at δ 2.9 (SCH_2) and a multiplet at 5.5 (C6-H). The n.m.r. spectrum of **5** exhibited two distorted triplets at δ 4.3 and 4.0 each integrating for one proton for OCH_2. A double doublet integrating for two protons at δ 2.83 was assigned to SCH_2. A multiplet for vinylic proton (C6-H) was also observed at δ 5.5.

The most striking difference in n.m.r. spectra of compounds **4** and **5** is the splitting pattern of OCH_2 and SCH_2 protons. The appearance of two distorted triplets and a double doublet in n.m.r. spectrum of **5** may be explained by assuming that the methylene protons bonded with the axially oriented oxygen atom are magnetically non-equivalent. Thus they behave differently towards the applied field and appeared at different chemical shift in the spectrum while methylene protons

attached to the sulphur atom are almost magnetically equivalent. The distorted triplets are due to pseudoequatorial and pseudoaxial protons (OCH_2; non-equivalent) resulting by the splitting with SCH_2 (magnetically equivalent). A double doublet for SCH_2 results by the splitting with pseudoequatorial and pseudoaxial protons (OCH_2; magnetically non-equivalent). The distortion in triplets may be consideted to the long range coupling.

The ketone **2** with β-mercaptoethanol in acetic acid using BF_3: Et_2O as catalyst at room temperature gave compounds melting at 135°C, **6**; 115°C, **7**; 118°C, **8** and a non crystallizable oil **9**. All these compounds were correctly analysed for $C_{29}H_{48}OS$ and i.r. spectra showed the presence of hemithioketal ring. The distinction between **6**, **7**, **8** and **9** was made possible on the basis of n.m.r. spectra.

On similar treatment ketone **3** afforded the compounds with were found identical in all respect to **6**, **7**, **8** and **9**.

We thank Prof. W. RAHMAN and Prof. M. S. AHMAD for providing necessary facilities and useful discussion. The assistance from CSIR and UGC (New Delhi) is gratefully acknowledged.

Experimental

All m.p.'s are uncorrected. I.r. spectra were measured on Perkin-Elmer 621 grating infrared spectrophotometry and n.m.r. spectra on a Varian A 60 instrument with $SiMe_4$ as internal standard. TLC plates were coated with silica gel and sprayed with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 60—80°C. Anhydrous sodium sulphate was used as the drying agent (n.m.r.: s, singlet; d, doublet; m, multiplet; t, triplet).

Reaction of 4,4-dimethylcholest-5-en-3-one 1 with β-mercaptoethanol

A mixture of **1** [5] (2.0 g) in dry benzene (100 ml) and β-mercaptoethanol (5 ml) (a few crystals of p-toluenesulphonic acid as acatalyst) was refluxed for 10 hrs. The reaction mixture was filtered. The filtrate was washed with water, $NaHCO_3$ solution and dried over sodium sulphate (anhydrous). The residue obtained after evaporation of the solvent was chromatographed over silica gel. Elution with light petroleum gave (150 mg) of **4**, recrystallized from light petroleum, m.p. 130°C Anal. Found C, 78.71; H, 11.11. $C_{31}H_{52}OS$ requires C, 78.81; H, 10.01%. ν max 1045 cm^{-1}. δ 5.5 m (C6-**H**), 4.2 distorted t (OCH_2), 2.9 t (SCH_2), 1.1 (C10—CH_3), 0.66 (C13—CH_3), 1.25, 0.90, 0.80 (other methyl protons).

Further elution with light petroleum yielded compound (130 mg), **5**, m.p. 140°C (recrystallized from light petroleum). Anal. Found C, 78.65; H, 11.17. $C_{31}H_{52}OS$ requires C, 78.81; H, 11.01%. ν max 1060 cm^{-1}. δ 5.5 m (C6-**H**), 4.3, 4.0 distorted ts (OCH_2), 2.83 d,d (SCH_2). 1.1 (C10—CH_3), 0.66 (C13—CH_3), 1.2, 0.90 0.80 (other methyl protons).

Reaction of cholest-5-en-3-one 2 with β-mercaptoethanol

The ketone (2) [6] (2.0 g) was treated with β-mercaptoethanol (5 ml) and BF_3:Et_2O (1 ml) in acetic acid (100 ml) and left at room temperature for 2 hrs. The solution was diluted with MeOH, poured into water and extracted with ether. The oily residue obtained after evaporation of the solvent was chromatographed over silica gel. Elution with petroleum:ether (20:1) gave **6**, which was recrystallized from light petroleum to obtained (30 mg) of m.p. 135°C (reported m.p. 136—37°C [2]). Anal. Found C, 78.29; H, 10.89. $C_{29}H_{48}OS$ requires C, 78.37; H, 10.81%. ν max 1060 cm^{-1}. δ 5.4 m (C6—H), 4.2 distorted t (OCH_2), 3.0 t (SCH_2), 1.01 (C10—CH_3), 0.68 (C13—CH_3), 0.91, 0.81 (other methyl protons).

Continued elution with petroleum:ether (20:1) gave **7** (35 mg), m.p. 115°C (recrystallized from light petroleum). Anal. Found C, 78.41; H, 10.78. $C_{29}H_{48}OS$ requires C, 78.37; H, 10.81%. ν max 1055 cm^{-1}. δ 5.2 m (C6—H), 4.18, 4.0 distorted ts (OCH_2), 3.0 d,d (SCH_2), 1.01 (C10—CH_3), 0.69 (C13—CH_3), 0.93, 0.83 (other methyl protons).

Further elution with petroleum:ether (5:1) yielded compound, recrystallized from light petroleum to obtained (40 mg) of **8**, m.p. 118°C. Anal. Found C, 78.45; H, 10.75. $C_{29}H_{48}OS$ requires C, 78.37; H, 10.81%. ν_{max} 1050 cm^{-1}. δ 5.6 s (C4—H), 4.17 distorted t (OCH_2), 2.64 t (SCH_2), 0.75 (C13—CH_3) 0.93, 0.83 (other methyl protons).

Elution with light petroleum:ether (1:1) gave a non crystallizable oil (40 mg), **9**. Anal. Found C, 78.33; H, 10.86. $C_{29}H_{48}OS$ requires C, 78.37; H, 10.81%) ν_{max} 1045 cm^{-1}. δ 5.63 s (C4—H), 4.3, 3.8 distorted ts (OCH_2), 2.85 d,d (SCH_2), 0.75 (C13—CH_3), 0.93, 0.83 (other methyl protons).

Reaction of cholest-4-en-3-one 3 with β-mercaptoethanol

Ketone **3** [6] (2.0 g) was treated with β-mercapto ethanol (5 ml) and BF_3:Et_2O (1 ml) in acetic acid (100 ml) and left at room temperature for 2 hrs. Usual worked up as **2** gave the compounds m.p. 135°C (30 mg), 115°C (35 mg), 118°C (45 mg) and a non crystallizable oil (40 mg) which were found identical in all respect to **6**, **7**, **8** and **9**.

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Allylic Bromination of Nitrosteroids

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Bromination of 3β-acetoxy-6-nitrocholest-5-ene (I), 3β-chloro-6-nitrocholest-5-ene (II) and 6-nitrocholest-5-ene (III) afford 3β-acetoxy-7α-bromo-6-nitrocholest-5-ene (IV), 3β-chloro-7α-bromo-6-nitrocholest-5-ene (V) and 4β, 7α-dibromo-6-nitrocholest-5-ene (VI) respectively IV and V on debromination furnish 3β-acetoxy-6-nitrocholesta-4,6-diene (VII) and 6-nitrocholesta-2,4,6-triene (VIII) respectively VII and VIII on refluxing with Zn – AcOH afford the ketones (IX) and (X) respectively IV, V and VI on treatment with Zn – AcOH at room temperature give the ketones (XI), (XII) and (XIII) respectively All the ketones (IX-XIII) are known in literature

Bromination of ketosteroids and subsequent dehydrobromination by base is frequently employed to create unsaturated centres in steroid molecule[1,2] We considered it expedient to prepare some nitrosteroids with bromine at α and β-positions and subject some of them to dehydrobromination with pyridine under reflux

Treatment of 3β-acetoxy-6-nitrocholest-5-ene (I)[3] in CCl_4 with N-bromosuccinimide (NBS) gave the bromo compound (IV) which analysed for $C_{29}H_{46}O_4NBr$ The IR spectrum of IV exhibited ν C – Br ~ 675 cm^{-1} and its PMR spectrum displayed a broad singlet at δ 5 08 for (C-7β-*H*, $W_{\frac{1}{2}} = 3$ Hz), indicating its equitorial configuration The bromine at C-7, therefore, is axial (α) oriented The configuration of bromine was further supported by its CD (negative cotton effect)[6,7] (λ253 nm) Similar treatment of 3β-chloro compound (II)[4] provided V with the same stereochemistry of bromine at C-7 as IV

Bromination of the parent 6-nitrocholest-5-ene (III)[5] under identical reaction conditions provided the dibromo compound (VI), the PMR spectrum of which exhibited two broad singlets at δ 5 05 and 5 56 for (C-7β-*H*, $W_{\frac{1}{2}} = 3$ Hz, equitorial) and (C-4α-*H*, $W_{\frac{1}{2}} = 4$ Hz) respectively suggesting axial configuration for C-7 and C-4 bromine atoms IV and V when refluxed in pyridine, provided the diene (VII) and triene (VIII) respectively The ketones (IX)[8] and (X)[9] were obtained from VII and VIII respectively by refluxing with Zn – AcOH while XI[10], XII[11] and XIII[12] were obtained from the compounds IV, V and VI by treatment with Zn – AcOH at room temperature

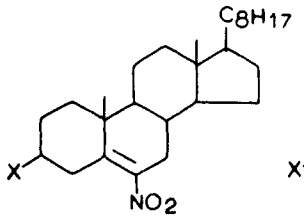
All melting points are uncorrected IR spectra (Nujol) were recorded on a Perkins Elmer 621 grating infrared spectrophotometer and PMR spectra on a Varian A60 instrument with TMS as internal standard CD curves were measured with Jasco J20 spectrophotometer TLC plates were coated with silica gel and sprayed with 20% aq perchloric acid Light petroleum refers to the fraction b p 60-80° Anhydrous sodium sulphate was used as the drying agent

Bromination of 3β-acetoxy-6-nitrocholest-5-ene (I)—To a solution of I (2 g) in carbontetrachloride (150 ml), NBS (2 g) was added along with few crystals of benzoyl peroxide as catalyst and the mixture refluxed for 3 hr The reaction mixture was cooled, filtered and the filtrate concentrated under reduced pressure to obtain a dark brown residue which was purified by column chromatography over silica gel (40 g) Elution with pet ether-ether (15 1) afforded 3β-acetoxy-6-nitro-7α-bromocholest-5-ene (IV) which recrystallized from pet ether (1 5 g), m p 165° (Found C, 63 0, N, 2 5, H, 9 0 $C_{29}H_{46}O_4NBr$ requires C, 63 45, N, 2 5, H, 8 3%), IR 1740 (CH_3COO), 1655 (C=C), 1515 and 1375 (C – NO_2), 675 cm^{-1} (C – Br), PMR δ 4 6 (*m*, 1H, C_3-H), 5 08 (*br*, 1H-C_7-H), 2 00 (*s*, 3H, CH_3COO), 1 18 (3H, C_{10}-CH_3), 0 73 (3H, C_{13}-CH_3), 0 83 and 0 91 (other methyl protons)

Bromination of 3β-chloro-6-nitrocholest-5-ene (II)—Bromination of II (2 g) was carried out as above to obtain 3β-chloro-7α-bromo-6-nitrocholest-5-ene (V) which recrystallized from light pet ether (1 4 g), m p 167° (Found C, 60 6, N, 2 6, H, 8 6 $C_{27}H_{43}O_2NBrCl$ requires C, 61 3, N, 2 6, H, 8 1%), IR 1660 (C=C), 1515 and 1375 (C – NO_2), 760 (C – Cl), 665 cm^{-1} (C – Br), PMR δ 4 0 (*m*, 1H, C_3-H), 5.12 (*br*, 1H, C_7-H), 1 2 (3H, C_{10}-CH_3), 0 73 (3H, C_{13}-CH_3), 0 83 and 0 93 (other methyl protons)

Bromination of 6-nitrocholest-5-ene (III)—Bromination of III (2 g) under similar conditions furnished 4β,7α-dibromo-6-nitrocholest-5-ene (VI) which recrystallized from light pet ether (750 mg), m p. 143° (Found C, 56 1, N, 2 4, H, 7 8 $C_{27}H_{43}O_2NBr_2$ requires C, 56 5, N, 2 4, H, 7 5%), IR 1625 (C=C), 1525 and 1375 (C – NO_2), 612 cm^{-1} (C-Br), PMR δ 5 58 (*br*, 1H, C_4-H), 5 05 (*br*, 1H, C_7-H), 1.55 (3H, C_{10}-CH_3), 0 71 (3H, C_{13}-CH_3), 0 83 and 0 91 (other methyl protons)

Dehydrobromination of IV and V with pyridine—IV/V (1 g) was refluxed with pyridine (100 ml) for 2 hr The reaction mixture was acidified with HCl and extracted with ether and the ethereal solution washed with water, aq sodium bicarbonate (5%) and water,

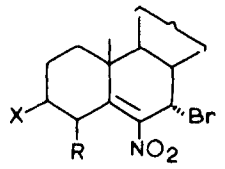


X

(I) OAc

(II) Cl

(III) H

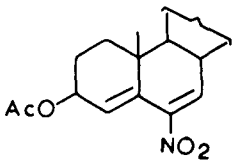


X R

(IV) OAc H

(V) Cl H

(VI) H Br



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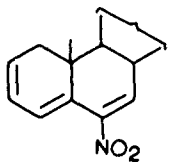
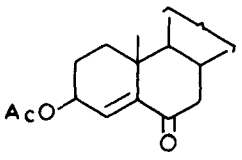


(VIII)



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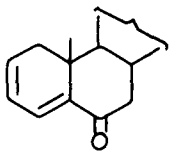
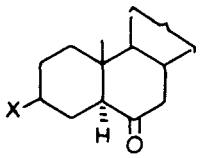


(X)



X

(XI) OAc

(XII) Cl

(XIII) H

and dried. Removal of the solvent gave a residue which was chromatographed over silica gel (20 g). Elution from pet. ether-ether (10:1 in the case of IV and 15:1 in the case of V) afforded 3β-acetoxy-6-nitrocholesta-4,6-diene (VII) and 6-nitrocholesta-2,4,6-triene (VIII). VII was recrystallized from pet. ether (600 mg), m.p. 103° (Found: C, 73.9; N, 2.9; H, 9.5. $C_{29}H_{45}NO_4$ requires C, 73.9; N, 3.0; H, 9.6%); IR: 1730 (CH_3COO); 1615 (C=C); 1510 and 1368 cm^{-1} (C–NO_2); PMR: δ 5.33 (*m*, 1H, C_3-H), 6.43 (*s*, 1H, C_7-H), 5.72 (*s*, 1H, C_4-H), 2.03 (*s*, 3H, CH_3COO), 1.05 (3H, C_{10}-CH_3), 0.75 (3H, C_{13}-CH_3), 0.83 and 0.91 (other methyl protons).

VIII was obtained as an oil (600 mg) (Found: C, 78.8; N, 3.4; H, 9.5. $C_{27}H_{41}NO_2$ requires C, 78.8; N, 3.5; H, 10.0%); IR: 1642 (C=C); 1540 and 1390 (C–NO_2); PMR: δ 5.9 (*br*, 1H, C_7-H), 6.5 (3H, C_4-, C_3- and C_2-H), 0.66 (2H, C_{13}-CH_3), 0.83 and 0.93 (other methyl protons).

Treatment of VII/VIII with Zn–AcOH—Treatment of VII/VIII (200 mg) with Zn–AcOH under refluxing condition afforded 3β-acetoxycholest-4-en-6-one (IX)[8] (150 mg) (m.p. and m.m.p. 109°) and cholesta-2,4-diene-6-one (X)[9] (160 mg), m.p. and m.m.p. 187-88°.

Treatment of IV, V and VI with Zn–AcOH—Treatment of IV/V/VI (250 mg) with Zn–AcOH at room temperature afforded 3β-acetoxy-5α-cholestan-6-one (XI)[10] (200 mg) m.p. and m.m.p. 128°, 3β-chloro-5α-cholestan-6-one (XII)[11] (200 mg) m.p. and m.m.p. 129° and 5α-cholestan-6-one (XIII)[12] (150 mg), m.p. and m.m.p. 99° respectively.

We thank Prof M S Ahmad for helpful discussion. One of us (SH) is thankful to the UGC, New Delhi for financial assistance.

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Synthesis of Steroidal Dinitro Conjugated Olefins†

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Synthesis of Steroidal Dinitro Conjugated Olefins†

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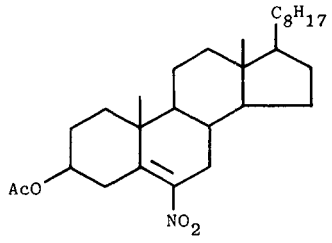
The synthesis of 3,6-dinitrocholesta-3,5-diene (3) in excellent yield from the readily accessible 3β-acetoxy-6-nitrocholest-5-ene (1) is reported.

Conjugated cyclic nitro-olefins are potentially both versatile and unique as synthetic intermediates for the stereoselective attachment of functional groups which can extend their activity to adjacent methylene groups, and also for annulation reactions.[1] We now report an easy method for the introduction of a dinitro conjugated olefinic system in steroids.



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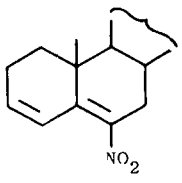

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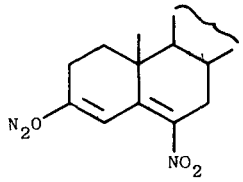

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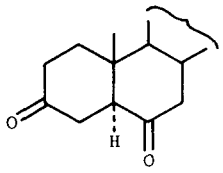
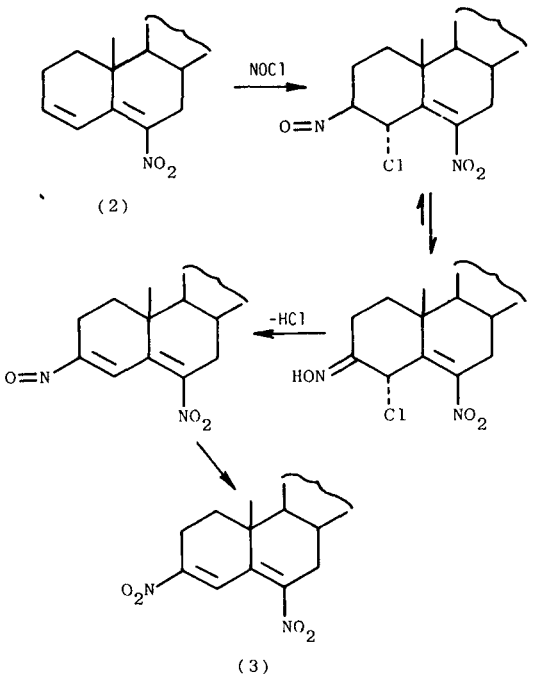


(4)

Reaction of 3β-acetoxy-6-nitrocholest-5-ene (1)[2] in dimethylformamide (DMF) with sodium azide followed by acidification with hydrochloric acid provided 6-nitrocholesta-3,5-diene (2).[3-5] Treatment of (2) with nitrosyl chloride in carbon tetrachloride resulted in 3,6-dinitrocholesta-3,5-diene (3). Compound (3) was also obtained by nitration of (2) with fuming nitric acid. The structure of compound (3) was established on the basis of its spectral properties and was supported by its conversion into 5α-cholestane-3,6-dione (4).[6] The mode of formation of the dinitro compound (3) is outlined in the Scheme.



(2) (3)

Scheme

Experimental

Reaction of 3β-Acetoxy-6-nitrocholest-5-ene (1) *with Sodium Azide–DMF.* – 3β-Acetoxy-6-nitrocholest-5-ene (1) (5 g) was dissolved in DMF (20 ml) and sodium azide (3 g) was added gradually with shaking. The reaction mixture was kept at room temperature for 48 h and then acidified with dilute hydrochloric acid and extracted with ether The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil which was crystallized from methanol to afford 6-nitrocholesta-3,5-diene (2) (4 g), m.p. 72 °C (lit.,[3-5] 72–73 °C); ν_{max} (Nujol) 1680 (C=C—C=C), 1508, and 1360 cm^{-1} (C—NO_2), δ 6.5 (1 H, d, *J* 10 Hz, 4-H), 6 1 (1 H, m, 3-H), 1.08 (3 H, s, 19-βCH_3), 0.70 (3 H, s, 18-βCH_3), and 0 95 and 0 83 (other side-chain methyl protons); $M^{+\cdot}$ 413 (Found: C, 78.4; H, 10.2; N, 3.4. Calc for $C_{27}H_{43}NO_2$: C, 78 45; H, 10 41; N, 3.38%).

Reaction of 6-Nitrocholesta-3,5-diene (2) *with Nitrosyl Chloride Gas.* – 6-Nitrocholesta-3,5-diene (2) (2 g) was dissolved in carbon tetrachloride and cooled in an ice–salt mixture. Nitrosyl chloride gas was then passed through the solution for 1 h after which time the solvent was removed under reduced pressure. The dark orange residue was dissolved in ether and the solution was washed successively with water, sodium hydrogen carbonate solution (1%), and more water, and then dried (Na_2SO_4). Removal of the solvent gave an oil which was crystallized from ethanol to afford 3,6-*dinitrocholesta*-3,5-*diene* (3) (1 75 g), m p 113 °C, ν_{max} (Nujol) 1651 (O_2N—C=C—C=C—NO_2), 1515, and 1380 cm^{-1} (C—NO_2), δ (CCl_4) 7.68 (1 H, s, 4-H), 1 10 (3 H, s, 19-βCH_3), 0 71 (3 H, s, 18-βCH_3), and 0 94 and 0 83 (other side-chain methyl protons) (Found: C, 70 7, H, 9 2, N, 6 1 $C_{27}H_{42}N_2O_4$ requires C, 70 74, H, 9 17, N, 6 11%).

Reaction of 6-Nitrocholesta-3,5-diene (2) *with Nitric Acid* – To a well stirred mixture of 6-nitrocholesta-3,5-diene (2) (3 g), glacial acetic acid (25 ml), and nitric acid (*d* 1 5,10 ml) below 20 °C was added sodium nitrite (1 5 g) gradually over 2 h Stirring was continued for a further 1 h and then the reaction mixture was poured into ice–water The yellow solid thus obtained was extracted into ether and the extract was washed with water, sodium hydrogen carbonate solution (5%), and more water, and then dried (Na_2SO_4). The solvent was removed to give an oil which was chromatographed over silica gel (40 g) Elution with light petroleum (b p. 40–60 °C)–ether (20 : 1) gave a yellowish solid which on crystallization from ethanol afforded the dinitro compound (3) (1.60 g), m.p. 113 °C, identical in all respects with the sample previously obtained

Treatment of 3,6-Dinitrocholesta-3,5-diene (3) *with Zinc–Acetic Acid* – Treatment of the dinitro compound (3) (500 mg) with zinc–acetic acid under reflux afforded 5α-cholestane-3,6-dione (4) (350 mg), m p and mixed m p 168 °C (lit.,[6] 169 °C).

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